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SPLENOPULMONARY PARENCHYMATOUS ANASTOMOSIS IN EXPERIMENTAL PORTAL HYPERTENSION IN DOGS AND MONKEYS

F. A. Remillard, B.A., M.D. (by invitation), P. E. Conen, M.B.B.S., M.R.C.P. (Lond.) (by invitation), and G. R. Walker, M.D., F.R.C.S.(C), Toronto, Ontario

THE PURPOSE of this work was an attempt to find an improved surgical treatment for portal hypertension in children. Baronofsky[1] gave an excellent historical summary of the different surgical treatments that have been used for portal hypertension. It was generally agreed that the portacaval anastomosis was the best operation in selected subjects. The vascular anastomoses used in the treatment of portal hypertension in adults are not usually possible in children (Linton,[11] Walker[21]). The veins are frequently too small, may be already thrombosed, or may be the site of congenital defects (Snavely[18]). Even if an anastomosis is technically possible, thrombosis is liable to occur (Hunt[8]).

Previous operations that have been tried were shunts of various types, including portacaval, lienorenal, and between the superior mesenteric vein and the vena cava, also miscellaneous operations which included gastrectomy and transesophageal ligation of varices (Phemister,[15] Gray,[4] Shumacker,[17] Jordan,[9] Macpherson[12]).

The first report of the use of the spleen for an anastomosis was by Holman.[7] He implanted the spleen in the muscles of the abdominal wall in an attempt to relieve portal hypertension in one patient and in several experimental animals.

From The Research Institute and Departments of Surgery and Pathology, The Hospital for Sick Children, Toronto, Ontario.

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Nylander and Turunen[14] reported the case of a patient with a traumatic diaphragmatic hernia containing the spleen, part of the stomach, and some of the intestines in the left chest. A large collateral circulation had developed between the spleen and the chest wall. This observation encouraged him to transpose the spleen into the chest on 3 patients whose reports were in the same paper. In 1958, Turunen and Laitinen[19] reported a follow-up of 2 of these 3 cases plus an additional case. Walker[20] reported a new procedure in which part of the spleen was embedded within the substance of the lung in 9 dogs, and a vascular anastomosis was demonstrated between the two tissues. In 1960, Hoffman[6] reported supradiaphragmatic transposition of the spleen in 3 patients with portal hypertension and also experiments of this nature in animals.

In all these reports a good anastomotic circulation developed when the spleen was transposed to the thorax. Since embedding the spleen in the lung provides a more intimate contact between the portal and systemic circulations than simply transposition of the spleen into the chest, the procedure described by Walker[20] has been further investigated and modified.

MATERIALS AND METHODS

Twenty-two adult mongrel dogs, weighing between 12 and 25 kilograms, and 11 young *Macaca cynomolgus* monkeys, weighing between 1.5 and 4 kilograms, were used.

Splenopulmonary Anastomosis.—At operation, a left thoracoabdominal incision was made and the abdomen was opened. The splenic pedicle was mobilized so that the spleen could be placed in the chest. The splenic vessels were carefully dissected, particularly where they branch into the 2 pedicles of the spleen. In dogs used in the early part of this work, the largest vein and artery and a portion of the spleen receiving these two vessels was preserved and the rest of the spleen discarded. In other dogs the spleen was divided by a wedge-shaped cut between the insertion of the two pedicles. This enabled one portion of the spleen to be retained in the abdomen after over-sewing the cut edge with a continuous suture. The portion of the spleen to be placed in the chest was reduced in size to approximately 5 by 2 by 1 cm. by removing the capsule and leaving only splenic pulp (Fig. 1, *A*).

The chest was opened and the diaphragm incised as far as the left central tendon where a small portion was removed to provide space for the splenic pedicle. A Satinski clamp was placed on the lower lobe of the left lung to act both as a retractor and a hemostat. An incision was made on the lateral surface of the left lower lobe and enlarged into the substance of the lung by blunt dissection (Fig. 1, *B*). The remnant of the spleen was brought into the thorax, placed into this bed, and the lung sewn over it (Fig. 1, *C*). The Satinski and the bulldog clamps were removed. The diaphragm was closed and the pedicle examined for pulsations (Fig. 1, *D*). The chest was sutured without drainage by the method described by Markowitz.[13] The abdomen was closed in layers.

In general, the dogs recovered quickly from this operation and usually were eating and drinking normally after 24 hours. They did not lose weight and by the end of 10 days were apparently normal. A few dogs had a slight cough for 3 or 4 days, and one dog had a minor wound infection which responded promptly to treatment. Thoracentesis was performed on one dog because of hemothorax.

Sponge Operation for the Production of Chronic Portal Hypertension.—During this simple operation, the portal vein between the entry of the pancreaticoduodenal vein and the liver was freed. A metal or plastic ring encircling a thin sheet of compressed sponge was

placed around the portal vein as close to the liver as possible. The sponge used was a mixture of synthetic and natural cellulose. Portal hypertension has been produced consistently by this method which has been described in more detail elsewhere (Remillard[16]).

Portal Vein Ligation.—Through a right subcostal incision, the portal vein and pancreaticoduodenal vein were identified and dissected free. The portal vein was ligated above the entry of the pancreaticoduodenal vein.

Portal pressures: Venous pressure readings were taken by the same operator, using the same apparatus, under uniform conditions. The pressures were taken with a spinal manometer connected to a 20 gauge needle by a polyethylene tube, 30 cm. in length. This apparatus was filled with heparinized saline. The polyethylene tubing was size 10.5 Fr. and measured 2.69 mm. internal and 3.50 mm. external diameter. The zero level of the spinal manometer was adjusted so that it was level with the entry of the portal vein into the liver. In each instance at least three readings were taken. The majority of these were made with the needle in the portal vein, although large mesenteric veins were used when the portal vein was not accessible because of adhesions.

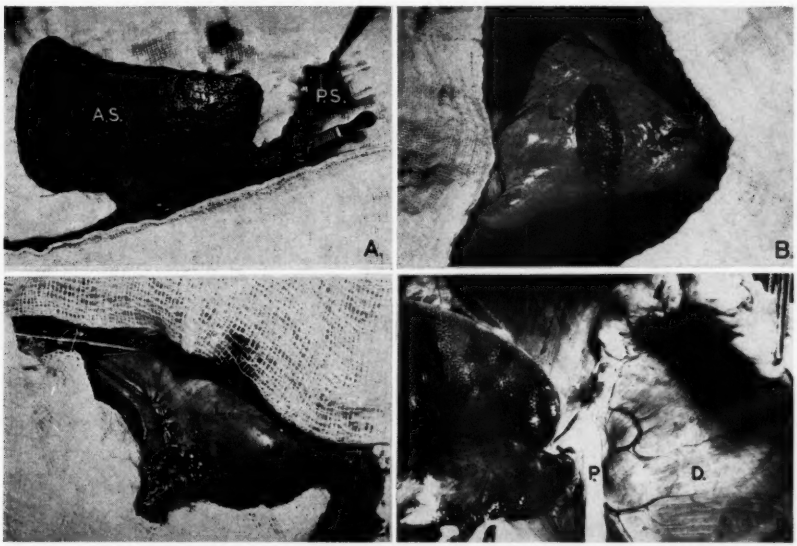

Fig. 1.—*A*, Spleen divided into abdominal (*A.S.*) and pulmonary (*P.S.*) parts. *B*, Lung showing splenic bed and Satinski clamp. *C*, Splenic pedicle (*P*) and lung (*L*) sewn over spleen. *D*, Undersurface of diaphragm (*D*) showing splenic pedicle 2 months later.

Venograms: These were done at least once on each dog at time intervals varying between 39 and 133 days following operation. Hypaque (90 per cent) was used as a contrast medium in all venograms and 20 to 25 ml. of this solution was injected gently, but rapidly, directly into the spleen or into a mesenteric vein through a 14 gauge needle, using a 20 ml. syringe. The x-ray study was made as the injection was completed (see Fig. 4).

Autopsy.—An autopsy was performed on all the animals, and corrosion casts and histologic sections were made of the sites of splenopulmonary anastomosis. The corrosion casts were prepared using colored solutions of vinyl chloride plastic in acetone (Bilbey[2]). A red solution was injected into the splenic artery, a yellow solution into the splenic vein, and a blue solution into the inferior pulmonary vein. After the plastic had set, a block of tissue for histologic examination was removed and the soft parts of the remaining specimen digested with hydrochloric acid.

RESULTS

Twenty-two dogs were operated upon but 7 died in the postoperative period following a splenopulmonary anastomosis. Three of these dogs died from anesthesia, one from shock, and 3 from hemorrhage. The hemorrhage was from the gastric artery in one dog and at the site of splenopulmonary operation in 2 dogs. These 7 dogs are not discussed further.

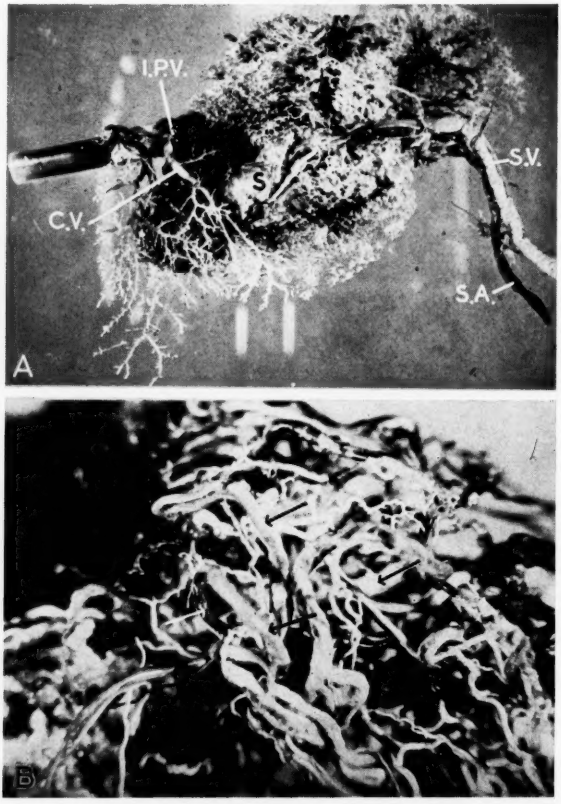

Fig. 2.—Corrosion casts of splenopulmonary anastomosis. *A*, Gross view. *B*, Low-power showing mixed colored plastics.

C.V.—Collateral vessels. *I.P.V.*—Inferior pulmonary vein. *S.*—Spleen. *S.A.*— Splenic artery. *S.V.*—Splenic vein.

Splenopulmonary Anastomosis.—Results were analyzed from 4 dogs in which only a splenopulmonary anastomosis was performed. A functioning anastomosis was only present in the one dog in which both splenic vessels were patent. This anastomosis was demonstrated by a venogram 31 days after the original operation. In corrosion casts from this dog it was possible to trace the injected plastic from the splenic vein through the embedded spleen and into the inferior

pulmonary vein (Fig. 2, *A* and *B*). Histologic examination showed many large and small vascular channels in the loose fibrous tissue between the spleen and surrounding lung (Fig. 3, *B*).

The splenic artery was patent but the vein was thrombosed in the dog examined 38 days after anastomosis. Both vessels were occluded in 2 dogs at 51 and 83 days after anastomosis.

Conclusions: These results would suggest that unless some stimulus to the development and maintenance of an anastomosis is present, the splenic vein and artery tend to thrombose after 4 to 5 weeks.

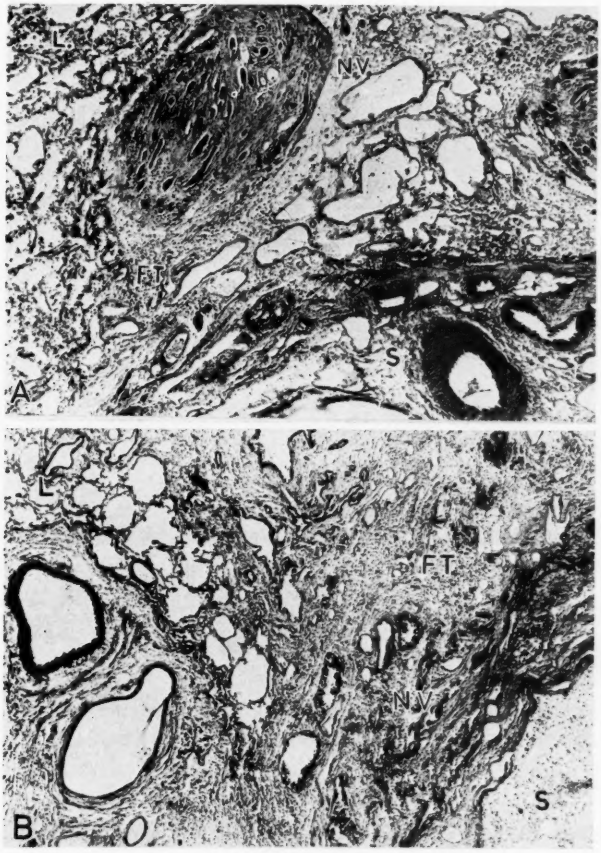

Fig. 3.—Splenopulmonary anastomosis (×100; reduced 4/5). *A*, Monkey. *B*, Dog. *F.T.*—Fibrous tissue. *L.*—Lung. *N.V.*—New vessels. *S.*—Spleen.

TESTS OF FUNCTION OF SPLENOPULMONARY ANASTOMOSIS

EXPERIMENT I.—To assess the ability of an established splenopulmonary anastomosis to protect the dog from the effects of acute portal hypertension produced by a one-stage portal vein ligation.

Two dogs in which a splenopulmonary anastomosis had been done had a second operation, one at 63 days and the other at 74 days after the anastomosis. At this second operation, a preliminary venogram was made followed by a second venogram while the portal vein was temporarily and partially occluded. Finally, a third venogram was made following complete ligation of the portal vein.

The anastomosis in the first dog was just visible in the preliminary venogram and was made easily visible with a temporary partial vein occlusion. The third venogram was made one hour after complete ligation and demonstrated an excellent anastomosis (Fig. 4). In spite of this, the dog died of acute portal hypertension and shock 110 minutes after complete occlusion of the portal vein. At autopsy both splenic vessels were patent and the presence of a good anastomosis was confirmed.

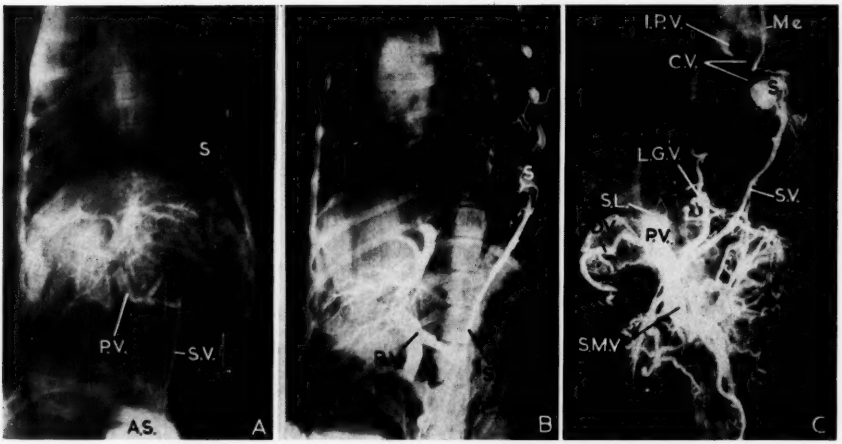

Fig. 4.—Splenopulmonary anastomosis followed by a one-stage portal vein ligation 63 days later. *A*, Normal venogram before ligation of portal vein. *B*, Venogram after partial ligation of portal vein. *C*, Venogram one hour after one-stage ligation of portal vein.

A.S.—Abdominal remnant of spleen. *C.V.*—Collateral vessels. *I.P.V.*—Inferior pulmonary vein. *L.G.V.*—Lieno-gastric artery. *Me.*—Mediastinal vein. *P.D.V.*—Pancreatico-duodenal vein. *P.V.*—Portal vein. *S.L.*—Site of ligation. *S.*—Pulmonary part of spleen. *S.M.V.*—Superior mesenteric vein. *S.V.*—Splenic vein.

All 3 venograms on the second dog failed to demonstrate a splenopulmonary anastomosis and no pulsation could be felt in the splenic pedicle. The dog died of acute portal hypertension one hour after complete portal vein ligation. Both splenic vessels were found to be thrombosed at autopsy.

Conclusion: Thus, anastomosis alone failed to protect the dog from acute portal hypertension.

EXPERIMENT II.—To assess the ability of an established splenopulmonary anastomosis to protect the dog from chronic portal hypertension produced by the sponge operation.

In 6 dogs the sponge operations were carried out from 32 to 147 days following the splenopulmonary anastomosis. During the sponge operation, the

splenic pedicle was checked for arterial pulsations and the anastomosis was tested by a venogram. Portal venous pressure was measured on all 6 dogs before the sponge was applied.

Two of these 6 dogs died of acute portal hypertension 5 and 10 hours following a modified sponge operation, in which additional veins were ligated including the large pancreaticoduodenal vein. These 2 dogs will not be discussed further.

The results in the other 4 dogs are shown in Table I.

Dog 84.—At the sponge operation, 32 days after anastomosis, portal pressure was 11.5 cm. of water and a venogram showed very small channels in the splenopulmonary anastomosis. Twenty-one days later the portal pressure had risen to 34.0 cm. and a second venogram showed larger vessels in the anastomosis.

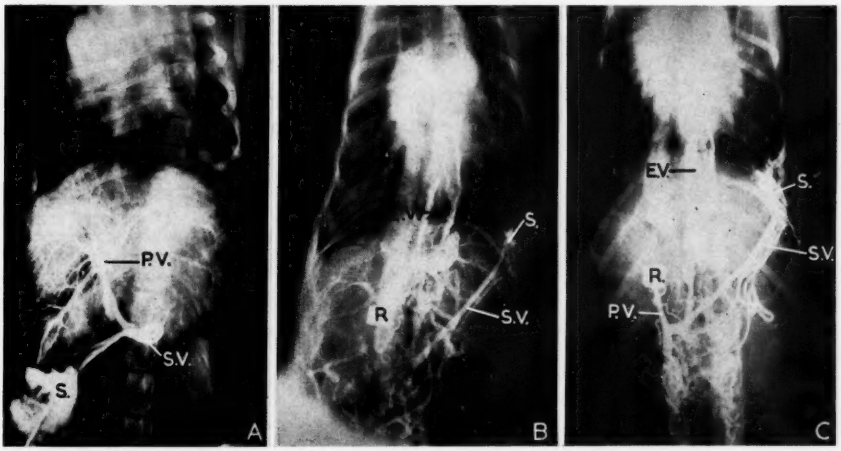

Fig. 5.—Venograms on dog with splenopulmonary anastomosis followed by a sponge operation 32 days later. *A*, Immediately before sponge operation. *B*, 21 days after operation. *C*, 45 days after sponge operation.

E.V.—Esophageal varices. *P.V.*—Portal vein. *R.*—Metal ring and sponge wrapping portal vein. *S.*—Spleen. *S.V.*—Splenic vein.

Forty-five days after the sponge operation, the pressure had fallen to 18.0 cm. of water and a third venogram showed the anastomotic vessels were even larger (Fig. 5). At autopsy, these findings were confirmed and the corrosion cast showed a very good anastomosis. It was possible that had this dog been allowed to survive longer its portal pressure might have returned to normal.

Dog 52.—During the sponge operation, 147 days after anastomosis, the portal pressure was 9.5 cm. of water. No arterial pulsation could be felt and a venogram failed to show an anastomosis. Sixty-two days later the portal pressure had risen to 29.5 cm. of water. At autopsy, thrombosis of both the splenic vein and artery was confirmed. Portal hypertension apparently developed because the splenopulmonary anastomosis was not functioning.

Dog 51.—At the sponge operation, 114 days after anastomosis, the portal

pressure was 11.0 cm. of water. A venogram did not outline the spleen but showed an anastomosis immediately above the diaphragm with a small vessel which ran into the mediastinum. Fifty-seven days later the portal pressure had risen to 21.0 cm. of water. The spleen was still not demonstrated and a splenic arteriogram showed a confluence of vessels around the diaphragm. These findings were confirmed by autopsy studies. The diaphragmatic collaterals were insufficient to protect the dog from developing portal hypertension.

TABLE I. RESULTS ON 15 DOGS WITH A SPLENOPULMONARY ANASTOMOSIS OPERATION

PROCEDURE	DOG	DAYS AFTER OPERATION		STATE OF SPLENIC VESSELS	STATE OF SPLENOPULMONARY ANASTOMOSIS
		FIRST	SECOND		
Splenopulmonary anastomosis only	90	31		Both patent	Good anastomosis
	80	38		Vein thrombosed; artery patent	No anastomosis
	86	51		Both thrombosed	No anastomosis
	58	83		Vein thrombosed; artery patent	No anastomosis
Splenopulmonary anastomosis and later portal vein ligation	92	63		Both patent	Good anastomosis
	83	74		Both thrombosed	No anastomosis
Splenopulmonary anastomosis and later sponge operation	84	77	32	Both patent	Good anastomosis
	52	209	147	Both thrombosed	No splenopulmonary anastomosis
	51	171	114	Vein to mediastinum; artery to diaphragm	No splenopulmonary anastomosis; unintentional anastomosis
	57	187	123	Vein to liver; artery patent	No splenopulmonary anastomosis; unintentional anastomosis
	65	116	Died at second	Results not included	
	56	133			
Sponge operation and later splenopulmonary anastomosis	71	113	53	Both patent	Good anastomosis
	74	105	51	Both patent	Good anastomosis
	69	131	45	Both patent	Good anastomosis

Dog 57.—During the sponge operation, 123 days after anastomosis, the portal pressure was 8.5 cm. of water, and 64 days later was still only 12.0 cm. Before sacrifice, a venogram showed complete occlusion of the portal vein but no dye was seen entering the lung. It also demonstrated a direct connection between the splenic vein and the liver. No portal hypertension developed in spite of failure of the splenopulmonary anastomosis because an unexpected anastomosis had developed.

Conclusion: When the delay between splenopulmonary anastomosis and sponge operation is too long, the splenic vessels may thrombose. These dogs then develop portal hypertension similar to that of normal dogs after the sponge operation.

EXPERIMENT III.—To assess the ability of subsequent splenopulmonary anastomosis to correct portal hypertension previously induced by the sponge operation.

In this series of 3 dogs the sponge operation was performed on the portal vein. Forty-four to 53 days following this, a splenopulmonary anastomosis was done.

Dog 71.—At splenopulmonary anastomosis, 53 days after the sponge operation, the portal pressure had risen from 10.5 cm. to 25.0 cm. of water. A venogram showed almost complete occlusion of the portal vein. Thirty-eight days later, the pressure had risen slightly to 30.0 cm. of water, and 60 days after the anastomosis, it had fallen to 14.5 cm. of water.

The slight increase in portal hypertension to 30.0 cm. of water was due to complete occlusion of the portal vein. During the last 22 days, a better splenopulmonary anastomosis had developed and reduced portal pressure to 14.5 cm. A good anastomosis was demonstrated at autopsy.

Dog 74.—During splenopulmonary anastomosis, 52 days after sponge operation, the portal pressure had risen from 9.5 cm. to 23.5 cm. Fifty-four days later, the pressure had fallen to 13.5 cm. of water. A venogram demonstrated a good anastomosis which was confirmed at autopsy, by a corrosion cast.

Dog 69.—At the sponge operation the portal pressure was 10.5 cm. of water. Forty-five days later, at splenopulmonary anastomosis, the pressure was 11.0 cm. A venogram showed only partial occlusion of the portal vein.

At sacrifice 86 days after the second operation, the portal pressure was normal at 8.5 cm. of water. The portal vein was narrowed but not occluded, and a good splenopulmonary anastomosis was demonstrated. It is probable that the narrowing of the portal vein was sufficient to develop the anastomosis between the spleen and the lung but not sufficient to produce portal hypertension.

Conclusion: In these 3 dogs it has been demonstrated that in the presence of portal vein obstruction, a good anastomosis could be obtained between the spleen and the lung. In the 2 dogs with portal hypertension, a very satisfactory reduction in portal pressure was obtained.

SPLENOPULMONARY ANASTOMOSIS IN MONKEYS

The anatomy of the portal system and the lungs of the *Macaca cynomolgus* monkey was studied in 6 animals by dissection and corrosion casts (Fig. 6). The findings were the same as those of Hartman and Strauss[5] who made a detailed study of the anatomy of the *Macaca rhesus.* A major difference between the spleen of a monkey and a dog was that in the monkey the pedicle was short and had a single artery and vein entering the spleen at about its mid-point. The proximal part of the pedicle was closely related to the pancreas and there was a ligament connecting the spleen to the left kidney. These differences made it more difficult to prepare a sufficient length of splenic pedicle to reach the lung without tension.

The splenopulmonary anastomosis in monkeys was tested by a subsequent one-stage portal vein ligation and compared to this ligation done on normal

monkeys. The anastomosis was not tested with a procedure for producing chronic portal hypertension since this takes many months and many operations (Laufman[10]).

One-Stage Portal Vein Ligation on Control Monkeys.—This was performed on 4 normal monkeys. The portal pressure in the portal vein and in a small mesenteric vein were found to be equal and this smaller vein was used in other monkeys since the bleeding was easier to control, particularly when acute portal hypertension developed. A second portal pressure was measured 10 minutes after portal vein ligation. This time interval was chosen since, in 1950, Child[3] reported that, after one-stage portal vein ligation in monkeys, the portal pressure rose rapidly to a maximum in about 10 minutes. A third portal pressure was measured 2 days after ligation since Child also reported that the pressure returned to normal in about 10 days.

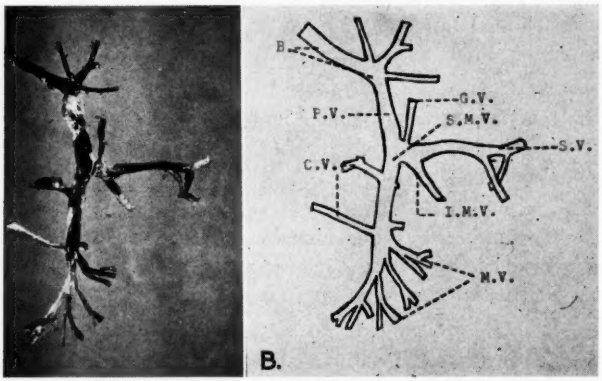

Fig. 6.—Normal portal system in monkey. *A*, Corrosion cast. *B*, Drawing of the same cast. *B.*—Bifurcation of portal vein. *C.V.*—Colic veins. *G.V.*—Gastric vein. *I.M.V.*—Inferior mesenteric vein. *M.V.*—Mesenteric veins. *P.V.*—Portal vein. *S.M.V.*—Superior mesenteric vein. *S.V.*—Splenic vein.

The first 2 monkeys, which were anesthetized with pentobarbital sodium (Nembutal) and ether, had initial portal pressures of 14.5 cm. and 13.5 cm. of water. Ten minutes after portal vein ligation these pressures had risen to 59.0 cm. and 57.0 cm. of water, respectively. These 2 monkeys died the night following operation and no cause of death was found at autopsy. Child has reported the death of monkeys after one-stage portal vein ligation with ordinary doses of pentobarbital sodium. It is not known whether our monkeys died because the liver was unable to detoxify the pentobarbital sodium or from shock due to acute portal hypertension.

Two additional control monkeys were anesthetized with ether only. The original portal pressure in one was 17.0 cm. and 10 minutes after portal vein ligation had risen to 51.0 cm. of water. This animal died 5 hours later and no cause of death was found. The original pressure in the other monkey was 17.5 cm. of water. This animal was already in shock 10 minutes after ligation of the

portal vein and it was not considered that the portal pressure reading of only 28.0 cm. of water was significant since it died 30 minutes after portal vein ligation.

Splenopulmonary Anastomosis.—Only slight modifications of the operation as used in dogs were necessary and there were no technical difficulties due to the operation itself. The animals were smaller and more difficult to anesthetize and the splenic pedicle was more difficult to prepare.

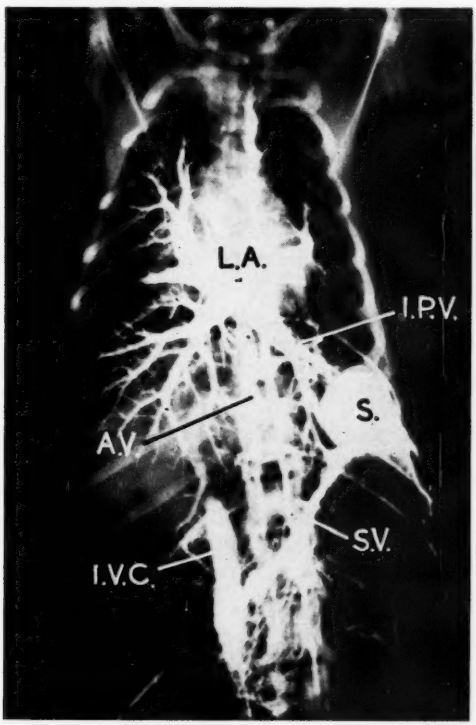

Fig. 7.—Postmortem venogram in monkey to show splenopulmonary anastomosis (Hypaque injected directly in splenic vein).
A.V.—Azygos vein. *I.P.V.*—Inferior pulmonary vein. *I.V.C.*—Inferior vena cava. *L.A.*—Left atrium. *S.*—Pulmonary part of spleen. *S.V.*—Splenic vein.

A splenopulmonary anastomosis was attempted in 7 monkeys and no major surgical difficulties were encountered during the operation. In spite of this, 5 of the 7 monkeys died from various causes; one from pneumothorax as the result of overinflation of the lungs, one from anoxia during anesthesia due to kinking of the endotracheal tube, one developed a brain abscess and septicemia as a result of an otitis media, and 2 monkeys died from hemorrhage due to perforation of the lungs by the sharp ends of the ribs. These last 2 monkeys seemed well at the end of the operation but died within 18 hours from a massive hemothorax.

The 2 surviving monkeys recovered satisfactorily from the operation and were apparently perfectly healthy.

Splenopulmonary Anastomosis Followed by One-Stage Portal Vein Ligation.—A second operation was performed 62 and 82 days later on the 2 healthy monkeys who survived splenopulmonary anastomosis. Their portal venous pressures were then 10.0 cm. and 16.0 cm. of water. A one-stage portal vein ligation was performed and after 10 minutes the pressures had risen to 28.0 and 48.5 cm. of water. The monkeys recovered satisfactorily from this operation and a laparotomy 2 days later showed that the portal pressures had fallen to 23.5 and 23.0 cm. of water. The monkeys were sacrificed at this laparotomy. A few hours after death, venograms were performed since x-ray facilities were not available in the operating theatre.

Anastomoses were demonstrated in both monkeys by venograms (Fig. 7), histologic sections (see Fig. 3, *A*), and corrosion casts. The anastomoses in the monkey with the lower pressure (28.0 cm. of water) was better and this had limited the elevation of portal pressure.

Conclusions: The splenopulmonary anastomosis in 2 monkeys protected them from the effects of sudden portal vein ligation. The species and the small size of these monkeys might have accounted for the failure of our control monkeys to survive one-stage portal vein ligation.

DISCUSSION

The splenopulmonary parenchymatous anastomosis operation has been performed on many dogs and some monkeys and, with experience, presents few technical difficulties. It should be even easier to perform on human beings than on the small monkeys used. The mortality due to the anastomosis operation itself in our series was low and in a human the mishaps causing death in our series would be avoided.

Only a small portion of the lung is lost by the presence of the anastomosis and it has been estimated that the deviation of part of the portal flow to the left side of the heart would cause no ill effect (Walker[20]). The splenic vein is preserved and should be available if later direct venous anastomoses are attempted.

This operation was originally devised as a temporary relief of portal hypertension in children until a formal venous anastomosis was possible at a later age. But it is quite probable that the anastomosis would continue to function in adult life and a later operation prove unnecessary.

A second use of this operation could be in adults in whom direct venous anastomoses have failed or in those with severe portal hypertension in whom attempts at direct anastomosis would be dangerous.

SUMMARY

1. An improved method of anastomosis between the spleen and the lung is described.

2. This improved splenopulmonary anastomosis reduced the portal hypertension produced experimentally in dogs by the sponge method.

3. Splenopulmonary anastomosis in monkeys lowered the pressure in acute portal hypertension and prevented death.

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(For Discussion, see page 779)

THE REGRESSION OF PULMONARY VASCULAR DISEASE AFTER THE CREATION OF PULMONARY STENOSIS

J. Francis Dammann, Jr., M.D., James A. McEachen, M.D.** (by invitation), W. M. Thompson, Jr., M.D.* (by invitation), Rodney Smith, M.D.** (by invitation), and William H. Muller, Jr., M.D.,* Charlottesville, Va., and Santa Monica, Calif.*

SINCE July, 1951, pulmonary stenosis has been produced surgically 66 times in 63 patients.[1, 2, 3] Patients selected for this palliative surgical procedure may be classified into three groups (Table I). Group I includes infants from 5 weeks to 2 years of age with large ventricular defects and high-output congestive failure not responding adequately to medical therapy, patients with large defects and equal systemic-pulmonary artery pressures, and patients with smaller defects, moderate elevation of pulmonary pressure, and a very high pulmonary blood flow. Group II includes patients of all ages who, at the time, could not have their defects corrected. These include patients with a single ventricle and those with simple ventricular defects who had creation of pulmonary stenosis prior to the advent of open-heart surgery. Group III includes older children with ventricular defects and evidence of progressive pulmonary vascular disease associated with increasing right ventricular hypertrophy, a decreasing left-to-right shunt, and less evidence of left ventricular and auricular hypertrophy.

Eleven patients in the total series have been re-operated upon for repair of their malformation and relief of the pulmonary stenosis. Four of these 11 patients did not survive. Two of them were found to have an atrioventricularis communis of such large dimensions that adequate repair was not feasible; one had multiple ventricular defects of both the membranous and muscular portions of the septum (some of which could be visualized only from the left ventricular side), the other died because of a central nervous system reaction related to cardiac bypass.

Six patients in Group I had corrective procedures 3 to 9 years after the initial stenosing procedure (Table II). In each, the indication for stenosing

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*From the Department of Surgery, University of Virginia School of Medicine, Charlottesville, Va.

**From Saint Johns Hospital, Santa Monica, Calif.

TABLE I. OVER-ALL RESULTS AFTER ATTEMPTED CREATION OF PULMONARY STENOSIS FOR DIAGNOSED VENTRICULAR DEFECTS

	OPERATIONS	DEATHS	PER CENT
Group I			
0-6 mo.	25	10	
6-12 mo.	5	1	
1-2 yr.	6	1	
	36	12	33
Group II			
Operable now (1961)	7	1	
Single ventricle	9	4	
Septum primum	2	2	
Interruption arch of aorta + VSD, PDA	3	2	
	21	9	43
Group III	8	2	25
Totals	65	23	35
Total Series (62 patients)			
Operations	65		
Deaths			
Before PA clamped		6	
Late		3	
Misdiagnosed and inoperable		4	
Others		10	
Total		23	

the pulmonary artery was that of high-output congestive failure which failed to respond to intensive medical therapy. At the time of the stenosing procedure, pulmonary artery pressures ranged from 85 per cent to 100 per cent of the systemic arterial pressure, and the ratio of pulmonary to systemic blood flow ranged from 1.9:1 to 5.8:1. The percentage drop in pulmonary artery pressure following the stenosis was 46 per cent to 65 per cent, and the percentage rise in aortic pressure was 0 to 40 per cent. Postoperative cardiac catheterizations

TABLE II. GROUP I*

		FIRST OPERATION					INTERVAL			SECOND OPERATION		
NAME	DIAG-NOSIS	AGE (MONTHS)	L:W	P.A.P. OR R.V.	P.A.P. / B.A.P.	P.F.: S.F.	DISTAL P.A.P.	O_2 SAT. %	P.F.: S.F.	AGE (YEARS)	P.A.P.	L:W
L. B.†	AVC	23	1.3	95/5	85%	5.8	20/3	89	1.8	9	35/10†	3.8
M. F.	VSD	20	1.7	65/35	76%	High	28/6	93	0.94	8⅓	?	3.8
M. F.	VSD	9	.95	90/7	95%	3.0	55/30	?	?	6	Norm.	?
K. B.	VSD	4½	1.8	92/2	100%	3.0	44/36	99	1.5	2½	22M	5.5
M. C.	VSD	3	1.25	90/8	100%	?	28/15	93	1.5	3	25	4.0
B. F.	VSD	3	—	59/2	100%	1.9	22/7	82	1.3	¾	45/0	4.5

Key:
First operation—creation of pulmonary stenosis.
Interval—cardiac catheterization between operations.
Second operation—surgical correction of cardiac defect.
L:W = lumen to wall ratio.
PAP = pulmonary artery pressure.
RV = right ventricular pressure.
BAP = brachial artery pressure.
PF:SF = ratio of systemic to pulmonary artery blood flow.
Distal PAP = pulmonary artery pressure distal to the artificial pulmonary stenosis.
O_2 saturation = systemic arterial oxygen saturation.
†Re-stenosed.

performed 2 to 6½ years after the original operation revealed a decrease (the lowest being 82 per cent) in peripheral arterial oxygen saturation, a decrease in the pulmonary/systemic flow ratio to under 2:1, and a further drop in distal pulmonary artery pressure. An analysis of the pressure tracings obtained from the distal pulmonary artery revealed a slope characteristic of a post-coaretation pulse wave; the more gradual or dampened the pressure tracing appeared, the more normal was the distal pulmonary artery pressure and lower the ratio of pulmonary to systemic blood flow.

In only 3 of the 6 patients are there adequate post-correction pulmonary artery pressure tracings. One (K. B.) registered a maximum mean pulmonary artery pressure of 22 mm. Hg simultaneously with a left auricular mean pressure of 14 mm. Hg. In a second patient (M. C.) the peak systolic pressure in the pulmonary artery was 25 mm. Hg. The third patient's (B. F.) right ventricular pressure several hours after correction was 45-50/2-8 mm. Hg, despite a left pneumothorax and left atelectasis. In a fourth patient (M. F.) distal pulmonary artery pressure initially was high due to left ventricular failure. What happened to it subsequently we do not know. In a fifth patient (M. F.) the surgeon stated that the pulmonary artery pressure was normal following closure of the defect. The sixth patient (L. B.) had large atrioventricularis communis which was irreparable and the pulmonary artery had to be re-stenosed.

Biopsies obtained from the lungs in each patient at the time of the palliative procedure revealed abnormally hypertrophied, muscular pulmonary arteries, with a small lumen-wall ratio (Fig. 1). Intimal changes were not present in any vessel. One patient (M. F.) retained some adventitial thickening at the time of correction, but the lumen-wall ratio was normal and the media and intima appeared normal (Fig. 2). A second patient (M. C.) had residual hypertrophy and tortuosity of the pulmonary artery but a normal lumen:wall ratio 3 years after the first operation. A lumen:wall ratio has not been obtained in the sixth patient (B. F.) but the pulmonary vasculature appeared completely normal.

For many years we have been interested in evaluating pulmonary vascular changes in patients with large ventricular defects. We have not encountered a single patient over the age of 2 years with a pulmonary artery pressure 75 per cent or above that of the aorta in whom the pulmonary vessels were not obviously hypertrophied and in whom there was not evidence of early intimal change. The stenosing procedure when done before the age of 2 prevents progressive vascular changes, clears cardiac decompensation, and permits a normal growth and development. The clinical improvement and normal pulmonary vessels in this group of patients have been sufficiently dramatic for us to consider narrowing the pulmonary artery in infants who are not in congestive failure. However, because we have had a mortality rate of 33 per cent, we have restricted our use of the procedure to patients in desperate need. Their need is demonstrated by the fact that 6 patients in the series died before the pulmonary artery could be isolated and all were in chronic congestive failure despite medical management.

The patients in the second group had either ventricular defects which could not be closed at that time, or more complex and still inoperable defects. Five patients, from 2¼ to 8 years of age at the time of their stenosing procedure, have been re-operated upon (Table III). Preoperatively, the pulmonary artery pressure varied from 55 to 100 per cent of brachial artery pressure. Pulmonary-to-systemic flow ratios varied from 2:1 to 4:1. In each patient there was evidence of an over-all left-to-right shunt, electrocardiographic evidence of biventricular increase in activity, vascular lung fields, and a cardiothoracic ratio ranging from 55 per cent to 63 per cent. By our present standards, this group of patients would be considered candidates for total correction of their defects

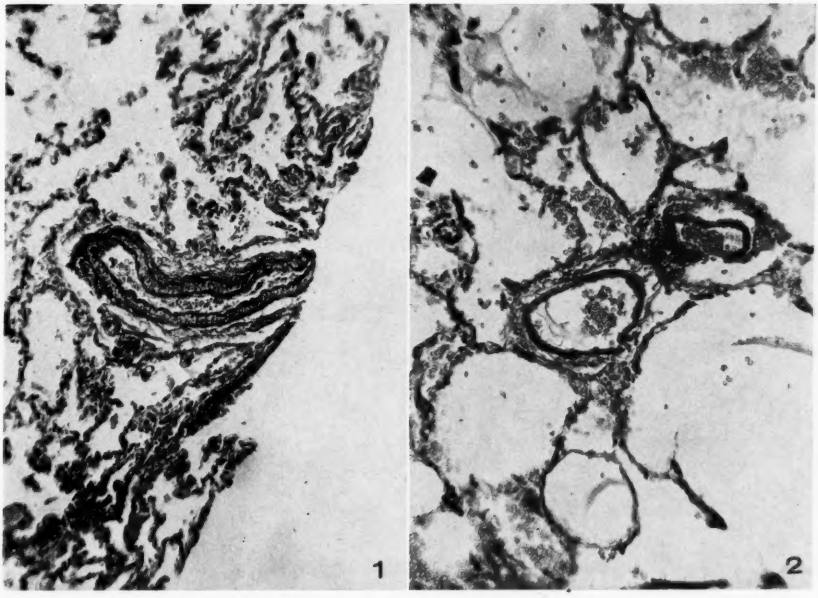

Fig. 1.—Photomicrograph (×580; reduced ⅓) of small pulmonary artery of patient K. B. at the time of narrowing the pulmonary artery.

Fig. 2.—Photomicrograph (×580; reduced ⅓) of small pulmonary artery of patient K. B. at the time of surgical correction of the defect.

TABLE III. GROUP II*

		FIRST OPERATION					INTERVAL CATH.			SECOND OPERATION		
NAME	DIAG-NOSIS	AGE (YEARS)	L:W	P.A.P. OR R.V.P.	P.A.P. B.A.P.	P.F.: S.F.	DISTAL P.A.P.	O_2 SAT. %	P.F.: S.F.	AGE (YEARS)	P.A.P.	L:W
J. J.	AVC	2⅓	1.3	96/0	100%	4.0	19/17 P.V.W.	98	1.1	4½	?	2.7
V. W.	VSD	5	1.1	64/21	55%	2.0	35/20	96	1.6	11	35/5	3.4
G. T.	VSD	7½	1.8	50/14	59%	?	25/11	91	1.7	13	42/7	2.8
R. M.	VSD	8	2.0	85/43	68%	2.0	35/10	93	1.5	14	40/22	4.55
J. L.	VSD	8	2.8	75/40	100%	2.5	21/6	73	0.4	14½	24/8	5.3

*_Key:_ Same as in Table II.

with the possible exception of one patient (J. J.) who, although only 2¼ years of age, demonstrated increasing pulmonary vascular resistance in the year following catheterization.

In these patients, the narrowed pulmonary artery produced as much of a drop in distal pulmonary artery pressure and as significant a rise in aortic pressure as in the group under 2 years of age. However, their postoperative course was not as dramatic. Postoperative catheterizations demonstrated a reduction in the ratio of pulmonary-to-systemic blood flow from the range of 4-2 to a range of 1.7-0.4, with 4 of the patients being between 1.1 and 1.7 and only one patient

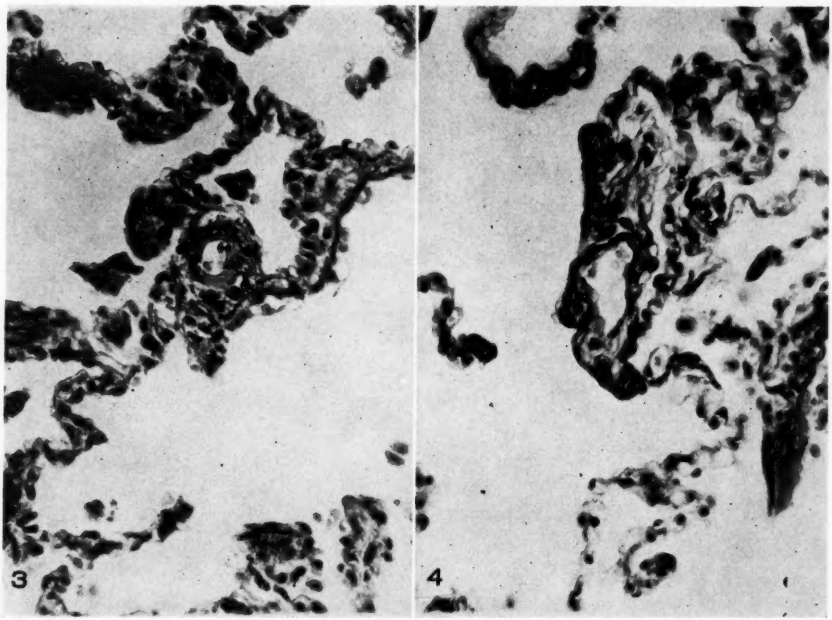

Fig. 3.—Photomicrograph (×580; reduced ⅙) of small pulmonary artery of J. L. at the time of narrowing the pulmonary artery. Note small lumen and thick media with only a little evidence of intimal thickening.

Fig. 4.—Photomicrograph (×580; reduced ⅙) of small pulmonary artery of J. L. at time of correction. Note thin-walled media and increase in size of lumen relative to wall thickness.

with cyanosis. Like the first group, the best results were in patients in whom the distal pulmonary artery tracing had a markedly dampened appearance with a blunted systolic peak.

Correction in this group of patients was performed from 5½ to 6½ years after the original stenosing procedure, except in one who had a lapse of 2 years. Two patients did not survive; one had a large atrioventricularis communis and one with a clear-cut and unavoidable reaction to cardiac bypass. In one patient, postoperative pulmonary pressures were not obtained; however, it was stated by the operating team that the pulmonary pressure seemed to be close to normal. Postoperative pulmonary artery pressures available in 4 patients

were approximately normal. These pressures were obtained at the time of operation with the chest open and the lungs partially collapsed. Postoperative catheterization and cardiac output studies, with the patient at rest and undergoing exercise, will be necessary before the degree of normalcy of the pulmonary vascular resistance can be ascertained. However, the fact that pressures in the distal pulmonary artery were within normal limits prior to correction while pulmonary blood flow exceeded systemic flow is strong argument that pulmonary vascular resistance was at least close to normal.

The significant difference between the two groups of patients as shown by the initial biopsies is twofold. In the second group, intimal changes were present and a few of the larger and markedly hypertrophied vessels were almost totally occluded (Fig. 3). Distal to these obstructed vessels, a process of thinning-out appeared to be taking place. Biopsies during the corrective operation revealed a surprising increase in the number of small pulmonary arteries seen per low-powered field and also an increase in lumen size of even those vessels with marked intimal change (Fig. 4). It cannot be determined whether the increase

TABLE IV

	FIRST OPERATION	SECOND OPERATION
Group I		
L. B.	Medial hypertrophy of large and small muscular arteries; arteriolar thickening	Negligible hypertrophy of large muscular arteries; other vessels normal
M. F.	Medial hypertrophy of all arteries except for some small vessels which were normal; intimal thickening of some	Within normal limits
M. F.*	—	—
K. B.	Medial hypertrophy of all arteries except for some small vessels which were normal	Within normal limits
M. C.†	—	—
B. F.†	—	—
Group II		
J. J.	Muscular arteries thickened	Hypertrophy of large muscular arteries; small vessels normal
V. W.	Medial hypertrophy of all vessels; some intimal thickening	Minimal medial hypertrophy of large muscular arteries; small vessels normal
G. T.	Moderate medial hypertrophy of large and small pulmonary arteries	Within normal limits
R. M.	Medial thickening of large and small muscular arteries; some intimal thickening; some thin, small vessels	Some hypertrophy of large muscular vessels; small vessels normal
J. L.	Medial hypertrophy of large muscular arteries; arterioles within normal limits	Within normal limits

*No second biopsy available for comparative evaluation.

†Second biopsy obtained at operation after Dr. Edward's review. Our pathologist described the second biopsy in M.C. as "normal, except for minimal large vessel thickening," in B. F. the second biopsy was described as "normal."

in the number of the small vessels represented new growth, a process of arterialization of precapillaries or merely dilatation of closed, but anatomically present, vessels. The increase in number, however, was very striking. A comparable increase has been noted in the experimental animal after the restoration of a normal pulmonary circulation some months after artificially produced pulmonary hypertension.

Evaluation of the differences between two sets of biopsies cannot help but be subjective when the observer is aware of the individual patient's course. It seemed wise to us, therefore, to have the biopsy material reviewed by an expert and impartial observer. Sections from each biopsy were all stained at one time, were coded and sent to Dr. Jesse E. Edwards, Chief of Pathology, Charles T. Miller Hospital, St. Paul, Minnesota. With his permission, we have listed his comments in Table IV according to the order in Tables II and III.

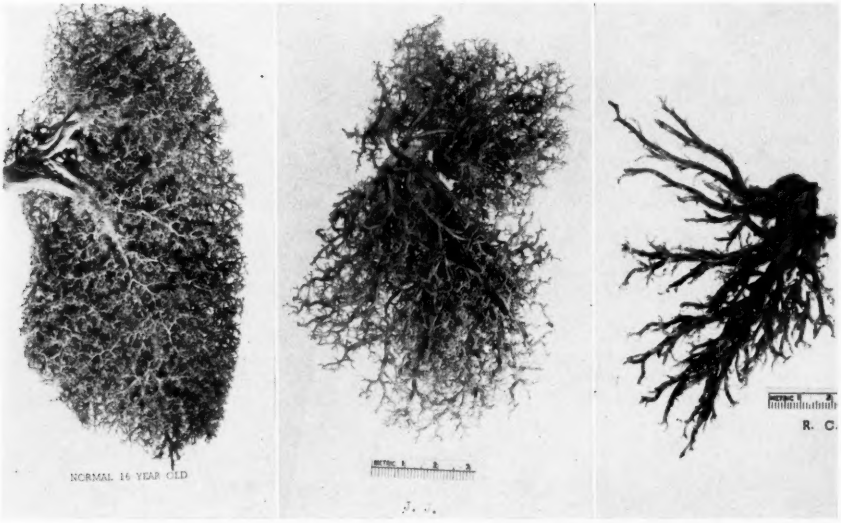

Fig. 5.—Plastic cast of arterial pulmonary circulation of 3 patients. *Left*—normal 16-year-old girl; *middle*—J. J., 2 years after the creation of pulmonary stenosis; *right*—R. C., patient with marked pulmonary vascular disease and ventricular defect, age 5.

The lumen-wall ratios obtained in the biopsies revealed a rise in ratio of 1.3-2.8 to 2.7-5.5. The child with the lowest initial ratio had the lowest final ratio. This poor improvement, we believe, is related to the short time interval between the original stenosing operation and the corrective operation. This period of time was 2 years, whereas the shortest period of time in the remaining cases was 5½ years. Nonetheless, a plastic cast (Fig. 5) of the pulmonary arterial bed demonstrates that the total cross-sectional area of pulmonary arteries is greater than that of a child of the same age with a comparable lesion. The arteries are still grossly tortuous, and the peripheral arborization normally seen as a fine feathery latticework extending along a smaller pulmonary artery is

irregular, blunted, incomplete, and decreased; however, it is superior to that of a child of the same age who had not been protected by pulmonary stenosis for the period of 2 years.

Two patients in our total series died prior to correction because of paroxysmal dyspnea comparable to that seen with tetralogy of Fallot. This occurred in a 5½-year-old boy 1½ years postoperatively, and in a 3¼-year-old boy 15 months after creation of pulmonary stenosis. Despite the reduction in pulmonary blood flow brought about by stenosis of the pulmonary artery, there was no significant change in the lumen-wall ratio in the first patient; there was a shift from a lumen-wall ratio 2.2 to 3.0 in the second patient. The state of the pulmonary vasculature in these 2 patients emphasizes the importance of permitting sufficient elapse of time between the stenosing and the corrective procedures.

TABLE V. GROUP III*

			UNCORRECTED						
NAME	DIAG-NOSIS	AGE (YEAR)	P.F.:S.F.	O_2 SAT. %	P. A. OR R. V. P.	P.A.P. / B.A.P.	DISTAL P.A.P.	DISTAL P.A.P. / PROXIMAL P.A.P.	RELATIVE PA-THOLOGY
G. C.	VSD	4	3	92	112/6	100%	45/40	49%	1
B. D.	VSD	9	1.24	90	105/75	100%	50/34	50%	3
W. M.	VSD	12	1.25	96	101/5	100%	55/40	52%	2
R. N.	VSD	8	2.1	92	76/50	100%	50/40	62%	4
R. J.	VSD	12	2	98	95/55	100%	70/55	78%	7
R. S.	VSD	13	< 1	?	110/60	100%	105/75	81%	5
G. B.	VSD	8	0.66	85	96/64	100%	75/50	100%	6
S. A. †	VSD	5½	0.5	74	155/64	100%	125/75	100%	8

Key:—Patients with surgical pulmonary artery stenosis but without correction of the defect. Distal PAP/proximal PAP = The final relationship of distal to proximal pulmonary artery pressure after surgical narrowing of the main pulmonary artery.

†Plus coarctation.

Thus, in this group of 5 patients, it would appear that banding the pulmonary artery in the presence of significant pulmonary vascular disease and significant pulmonary hypertension improved the pulmonary vascular bed. The degree of improvement depended upon the level to which distal pulmonary artery pressure dropped, the slope of the distal pulmonary pressure curve, the degree to which relative pulmonary blood flow was reduced, and, finally, the interval between the stenosing and corrective procedures. The best results were obtained in those patients carried for the longest period of time, in whom the pulmonary artery pressure had been reduced and dampened the most, and the flow reduced to a point where a reversal of blood flow occurred with exercise. Since the pulmonary vascular bed did not become completely normal in this second group of patients as contrasted to the first group, we would recommend early surgery provided, of course, the risk is not prohibitive.

The third group includes 8 patients with severe pulmonary vascular disease, 4 to 12 years of age, in whom pulmonary artery stenosis was created so that, over an extended period of time, the pulmonary vascular disease would subside and allow correction of the defect at a later date (Table V). These 8 patients had pulmonary blood pressures of 100 per cent or better of systemic pressure.

In each, evidence of left ventricular and left auricular enlargement was minimal or absent; serial electrocardiograms demonstrated a progressive increase in right ventricular activity and decrease in left ventricular activity; and serial x-ray studies revealed a steady decrease in heart size. The long, loud, coarse systolic murmur of the high-flow defect had been replaced by a nondescript short ejection murmur, and the pulmonary second sound had become increasingly accentuated and more widely split.

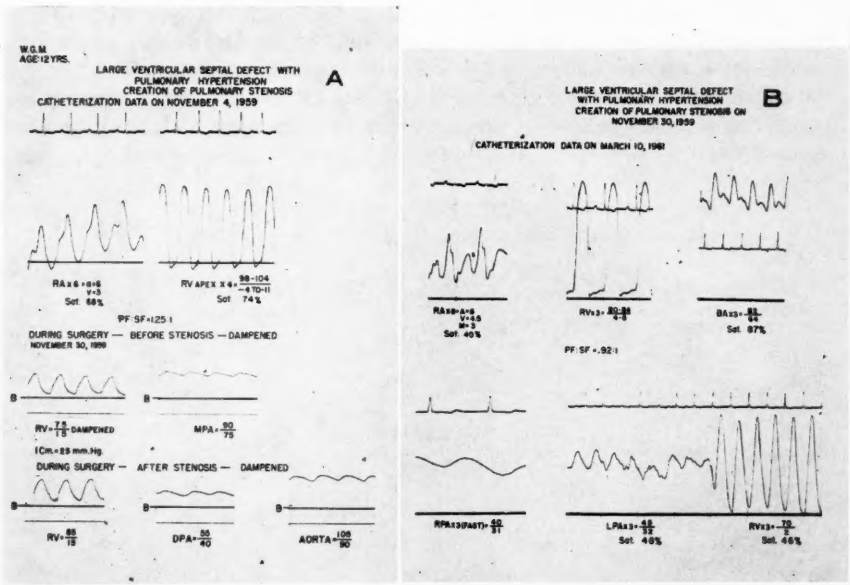
W.G.M.
AGE: 12 YRS.
LARGE VENTRICULAR SEPTAL DEFECT WITH PULMONARY HYPERTENSION
CREATION OF PULMONARY STENOSIS
CATHETERIZATION DATA ON NOVEMBER 4, 1959
A
DURING SURGERY — BEFORE STENOSIS — DAMPENED
NOVEMBER 30, 1959
DURING SURGERY — AFTER STENOSIS — DAMPENED
LARGE VENTRICULAR SEPTAL DEFECT WITH PULMONARY HYPERTENSION
CREATION OF PULMONARY STENOSIS ON NOVEMBER 30, 1959
B
CATHETERIZATION DATA ON MARCH 10, 1961

Fig. 6.—Catheterization data on W. M. *A*, Prior to creation of pulmonary stenosis. *B*, 1¼ years after stenosing procedure. Note that the mean pulmonary artery pressure is still above normal although less than would be expected for the reduction in PF:SF ratio if pulmonary vascular resistance remained fixed.

Of 3 patients in this group with an over-all right-to-left shunt, 2 succumbed in the postoperative period. One patient (S. A.), already mentioned, died 15 months postoperatively because of paroxysmal dyspnea. The second fatality (G. B.) was an 8-year-old boy with marked pulmonary vascular disease, who died of paroxysmal dyspnea soon after the operation. In neither was it possible to narrow the pulmonary artery enough to cause a drop in distal pulmonary artery pressure. Therefore, they were in no way benefited and it is not surprising that they died an acute pulmonary hypertensive death. The other 5 patients in this group had over-all left-to-right shunts as shown by cardiac catheterization, but 2 of these became cyanotic with exercise. Cardiac catheterization a year or more after creation of pulmonary artery stenosis in 2 patients revealed pulmonary-systemic blood flow ratios of under 1, a slight decrease in oxygen saturation at rest, and a distal pulmonary artery pressure of 10 per cent below that recorded at operation (Fig. 6). Although peripheral pulmonary pressures were not normal, they were significantly lower than if the vascular resistance had not decreased.

The lung biopsies from these 8 patients revealed a rather surprising spread of pathologic change. Lumen-wall ratios in the first 3 (G. C., W. M., B. D.) were between 1.5 and 2.0. In the other patients the lumen-wall ratios were not deemed valid since, in each, there was almost total obliteration of the lumen of large pulmonary vessels (Fig. 7), and distally dilated thin-walled vessels were produced. An attempt was made to grade the degree of vascular damage in the 8 patients. The progression of pulmonary vascular disease is first an increase in the number and degree of thick-walled, small pulmonary vessels, followed by a gradual increase in hypertrophy of the larger pulmonary

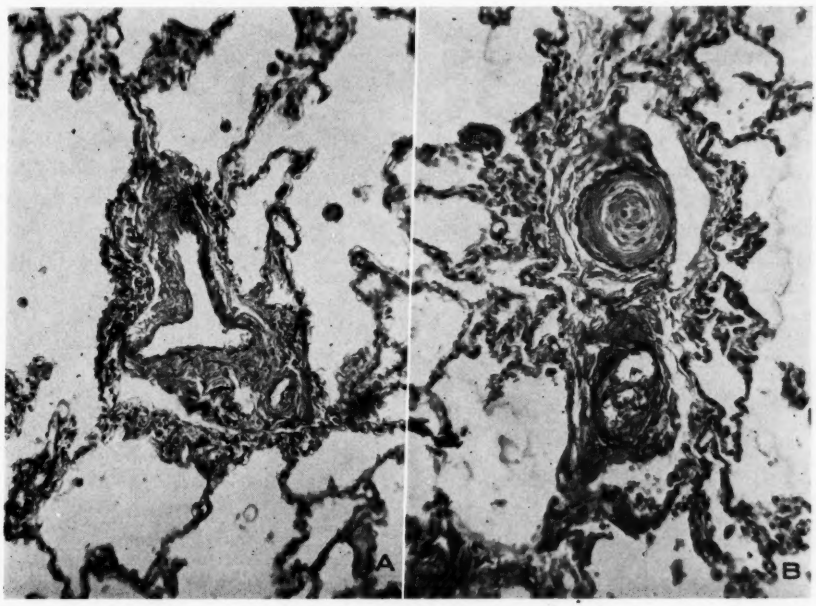

Fig. 7.—Photomicrograph (×245; reduced ⅘) of small pulmonary artery of (*A*) W. M. Note medial hypertrophy and minimal intimal change. *B*, G. B. Note intimal occlusion of muscular pulmonary artery and thinning of distal pulmonary artery.

vessels and the appearance of intimal damage. The number of hypertrophied small pulmonary arteries varies inversely with the duration of the hypertension and the degree of vascular disease. As pulmonary intimal damage progresses, there is more obstruction of the larger pulmonary arteries, thereby removing the stress from the distal pulmonary vessels. Consequently, an increasing number of dilated, thin-walled vessels are found. Thus, we used three criteria to judge the degree of vascular damage: (1) The number of hypertrophied small pulmonary arteries. (2) The relative incidence of obstructed vessels (it is self-evident that the more numerous the totally occluded vessels the more severe the pulmonary vascular disease). (3) The number of thin-walled, dilated vessels contrasted to the number of hypertrophied small vessels. With these

three criteria, the 8 cases in this series were analyzed and compared independently of the hemodynamic findings and without the knowledge on the part of the examiner of the identity of the patient.

In Table V the results of this comparison are given and these results are placed against the change in distal pulmonary artery pressure which was produced when the main pulmonary artery was narrowed. In patients with extreme pulmonary vascular disease we were unable to lower significantly distal pulmonary artery pressure which suggests that pulmonary flow was as low as could be tolerated and resistance was fixed. In patients with less pulmonary vascular disease, a significant reduction in distal pulmonary artery pressure

Fig. 8.—Cast of the pulmonary arterial bed of an experimental animal subjected to a high pulmonary artery pressure. Note the normal arborization is totally destroyed except in one portion which was protected by a kink in the parent artery.

could be obtained which implies that pulmonary flow could be lowered slightly and, more important, pulmonary vascular resistance was not fixed but was made up of increased vascular tone. Just as the small, hypertrophied pulmonary vessels lose tone, dilate, and become thin-walled when a parent large pulmonary artery becomes partially obstructed, so all pulmonary vessels beyond a main pulmonary artery stenosis will dilate and lose tone. The degree to which they can dilate will depend upon the amount of intimal damage. As we have seen

in Group II we would expect in this third group of patients to see a marked increase in the number of small vessels and a dilatation of even those vessels with significant intimal damage. This thesis remains to be proved. We believe that it will be proved, provided sufficient time is permitted to elapse between the stenosing and the corrective procedures. At least 6 years should be allowed. Thus, it will be a matter of 3 years before re-operation can be considered in any patients in this group.

The mechanism whereby vascular tone is reduced lies, we believe, in the reduction in stimulus which is brought about by dampening the pulse wave or reducing the systolic peak. In our total series, the best results have been in patients in whom the distal pulmonary artery pressure tracing appeared the most dampened. It seems logical, then, that the explanation of failure to improve after closure of a reverse ductus or balanced ventricular defect is that the pulse wave is not altered by closure of the defect and, hence, the stimulus for a high vascular tone remains. In the systemic circulation, coarctation of the aorta offers a comparable problem. An examination of vessels proximal and distal to a severe coarctation will demonstrate that the proximal vessels are thick-walled, with a small lumen, and subject to intimal change, whereas the distal vessels are thinner, have larger lumens, and less intimal change. And yet, mean and diastolic pressures above and below the coarctation are not markedly different. Furthermore, there are a few instances described in the literature[4, 5, 6] in which, following resection of the coarctation, the increased stress on the distal vessels brought about by the increase in systolic peak pressure, led to an acute arteritis. A similar arteritis can be produced in the pulmonary arteries of the experimental animal when the lung is subjected to an acute increase in pressure (Fig. 8). The stress exerted by stretch of a vessel wall, if severe enough, causes rupture and an arteritis. A lesser stress produces hypertrophy of a vessel wall and varying degrees of intimal damage. A high pulse pressure with a high systolic peak exerts the greatest stretch. Consequently, if pulse pressure is narrowed and the systolic peak lowered, stress is reduced and disuse atrophy of hypertrophied vessels may result.

By reducing pulse pressure and the systolic peak of the distal pulmonary arteries in this series of patients we believe that in the younger patients, progressive changes were prevented and, in older patients, were reversed.

SUMMARY AND CONCLUSIONS

During the past 10 years we have stenosed the pulmonary artery in 63 patients in whom the diagnosis of a simple or complex large ventricular defect had been made. The indications for surgery were congestive failure or evidence of progressive pulmonary vascular disease. The patients were classified into three groups: (1) children under 2 years with evidence of failure, (2) patients with lesions which at the time could not be corrected, and (3) older children with correctable ventricular defects but with markedly elevated pulmonary vascular resistance who would not tolerate curative surgery.

Eleven of these 63 patients have since been operated upon and their defects

corrected. There were four fatalities, three due to the complex nature of the malformation and one to a reaction to use of the heart-lung machine. Among the 6 patients in Group I, the pulmonary bed was found to be normal in the 5 in whom biopsy material was available. Hemodynamic studies were in agreement. There were 5 patients in Group II whose defects were corrected. Hemodynamic data indicated a reduction in pulmonary vascular resistance. Final pulmonary artery pressures were close to normal and a comparison of the lung biopsy material indicated a marked improvement in the pulmonary vascular bed.

No patients in Group III have been re-operated upon because sufficient time for vascular healing has not elapsed. However, interval catheterizations suggest a significant decrease in resistance in the 2 patients studied.

The data obtained in this series suggests that the stress which produces vascular disease is removed when the distal pulmonary artery pressure is lowered. The pulse pressure decreased and the systolic peak dampened out.

We would like to express our appreciation to Dr. Denton A. Cooley and Dr. Jerome Kay for follow-up information on 2 of the patients in this series.

ADDENDUM

Since this paper was presented, 2 additional patients had intracardiac lesions corrected and the area of pulmonary artery stenosis has been resected. One patient (J. M. C.) belongs in Group I. The second patient (P. M.) belongs in Group II. In both patients, pulmonary vascular changes had disappeared, except for minimal adventitial thickening, and the postoperative pulmonary artery pressures were within normal limits.

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(For Discussion, see page 779)

THE EFFECT OF LOW MOLECULAR WEIGHT DEXTRAN UPON THE BLOOD FLOW DURING EXTRACORPOREAL CIRCULATION

Christopher T. Drake, M.D. (by invitation), Fidel Macalalad, M.D. (by invitation), and F. John Lewis, M.D., Chicago, Ill.

MOST methods of cardiac surgery employ some degree of hypothermia. This is not necessary when a pump-oxygenator system is used but assumes vital importance in any method which includes a period of circulatory arrest. One such method is autogenous oxygenation which has been of interest to us for some time. This method includes a period of cooling followed by a period of circulatory arrest during which the correction of the cardiac defect takes place.[3, 8, 9, 16] Surface cooling has several disadvantages[4, 5]; therefore, a blood heat exchanger is employed.

The purpose of direct blood cooling is to provide rapid reduction of body temperature with consequent decrease in metabolic demands.[1] Other factors being equal, the rate of induction of hypothermia by direct blood cooling depends on the performance of the blood heat exchanger and the systemic flow rate. The latter decreases as the body temperature falls,[2] however, and consequently the rate of cooling slows. This is of particular importance when profound hypothermia to levels of 10° to 15° C. is desired. If the systemic flow rate cannot be maintained near its normothermic value, the time required to achieve such low temperatures is prolonged to an hour or more. Furthermore, if blood flow decreases too much, it may be inadequate to supply tissue oxygen demands.[7] We have therefore attempted to maintain systemic blood flow near its normothermic level and have tested the effect of the administration of low molecular weight dextran (LMWD*), comparing it to that of blood.

METHODS AND MATERIALS

Adult mongrel dogs, weighing 9 to 18 kilograms, were anesthetized with intravenous Pentothal. An endotracheal tube was inserted and connected to an automatic respirator supplying room air.

An aneroid manometer connected to an arterial catheter registered arterial pressure. Systemic venous pressure was measured by a saline manometer connected to a catheter in the inferior vena cava.

From the Department of Surgery, Northwestern University Medical School, Chicago, Illinois.

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*Rheomacrodex: 10 per cent solution provided by the Pharmacia Co., Uppsala, Sweden, Average molecular weight 35,000 to 40,000; intrinsic viscosity—0.19.

The chest was entered through the left fourth intercostal space. Following heparinization (2 mg. per kilogram), catheters were placed in the heart and femoral artery, as previously described.[11, 16] By means of these catheterizations and a blood heat exchanger interposed in the systemic circuit, a two-pump bilateral bypass circuit (Fig. 1) providing autogenous oxygenation and direct blood cooling was achieved.

Volume sensitive automatic controls limited the delivery of the De Bakey pumps to only as much blood as drained into the pump reservoirs[14] and maintained a constant small (1,000 c.c.) extracorporeal volume (Fig. 1).

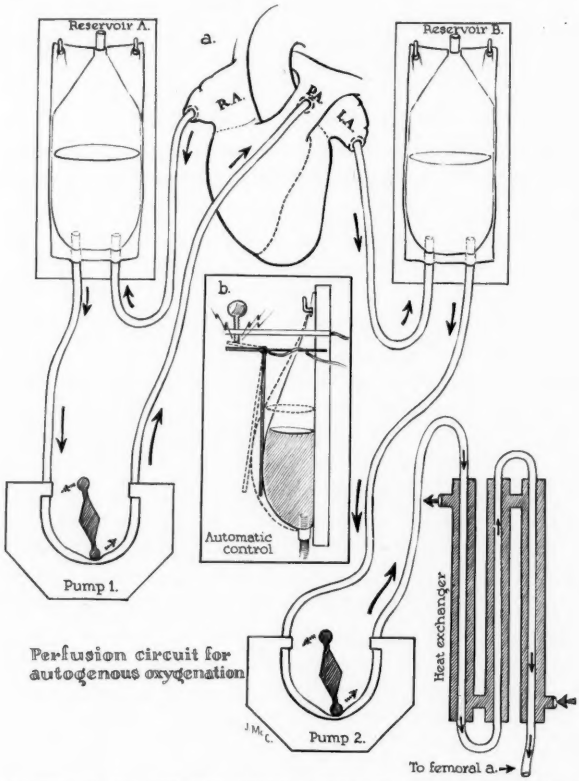

Fig. 1.—Diagram of the perfusion circuit. Blood is drained by gravity from the right atrium into reservoir *A* and pumped by *Pump 1* into the pulmonary artery. After pulmonary oxygenation, it is drained from the left atrium into reservoir *B* and pumped by *Pump 2* through the heat exchanger into the femoral artery.

The heat exchanger consists of several sections of thin stainless steel tubing. Each section is enclosed within a large tubular jacket. Both inner and outer segments of tubing are connected to their mates in series. Blood flows through the inner tubing in a single continuous stream the direction of which is opposite to that of the cooling solution flowing in the outer jacket. A thermistor probe monitors the blood outflow temperature continuously. A heat exchanger such as this permits the use of jacket temperatures of −15° to −30° C. and provides outflow temperatures of 3° to 7° C. at flow rates up to 3 L. per minute. The cooling rate thus becomes more dependent upon the flow rate. Jacket temperatures of 50° to 60° C. provide outflow temperatures of 38° to 41° C. during rewarming. Outflow temperature regulation is achieved by manual control of the flow rate of the jacket solution through the exchanger. Fig. 2 shows the pumps, reservoirs, and heat exchanger.

Appropriately placed thermistor probes provided continuous monitoring of the esophageal, cardiac, and muscle temperatures. A tapered flow rotameter, calibrated for blood, monitored the systemic flow rate.

Blood oxygen was determined by the Van Slyke method and pH was determined with a Beckman pH meter. Hematocrit and plasma hemoglobin were also determined.

To date, 52 bypass experiments have been done. Nineteen of these animals served as controls and received no blood or colloid prior to or during the bypass. Twenty-eight dogs received 10 to 12.5 c.c. per kilogram of low molecular weight dextran just prior to the bypass. Five dogs received an equal amount of blood just before the bypass.

An attempt was made to cool all animals to an esophageal temperature of 10° C., but cooling was stopped if the temperature fell less than one degree per 5 minutes. The animals were then immediately rewarmed to 33° to 37° C. After removal of the catheters, polybrene was given to neutralize the heparin.

Artificial respiration was discontinued when the animals could breathe spontaneously. A suction chest tube was used for 3 to 4 hours postoperatively and a Therm-O-Rite blanket warmed the animals to 35° C. when necessary. Blood was administered as indicated and penicillin was used intrapleurally and intramuscularly. Penicillin treatment was then continued for 3 to 4 days postoperatively.

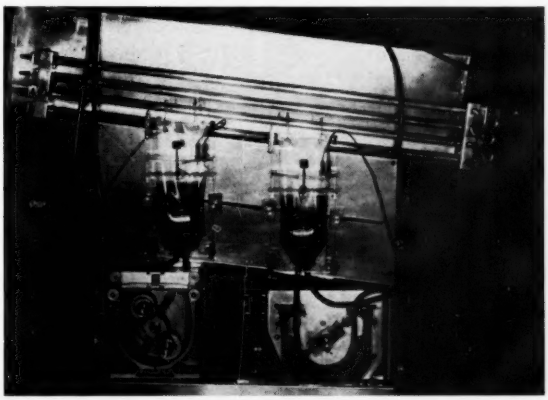

Fig. 2.—Photograph of the automatically controlled pumps, venous reservoirs, and heat exchanger.

RESULTS

1. *Hemodynamic Findings.*—

a. *Systemic flow rates*: The changes in the average flow rates of the three groups of animals are shown on Fig. 3. The administration of LMWD prior to the bypass resulted in significantly higher initial flow rates as compared to the control group ($p = 0.0139$). Blood administration, on the other hand, had no significant effect. The flow rate began to decrease progressively in all animals as the esophageal temperature fell, and the lowest flow rates were obtained at 10° C. The LMWD recipients had significantly higher flow rates by the end of cooling than the control group ($p = 0.0001$) or the blood group ($p = 0.009$). The administration of blood, although it did not significantly affect the initial flow rate, did help maintain higher flow during cooling than that of the controls ($p = 0.0193$).

The flow rates began to increase within 2 to 3 minutes after rewarming was initiated. The peak values were obtained between 25° and 30° C., after which the flow rate decreased slightly. The average flow rate of the LMWD recipients during rewarming was significantly higher than that of the other groups ($p = 0.0006$).

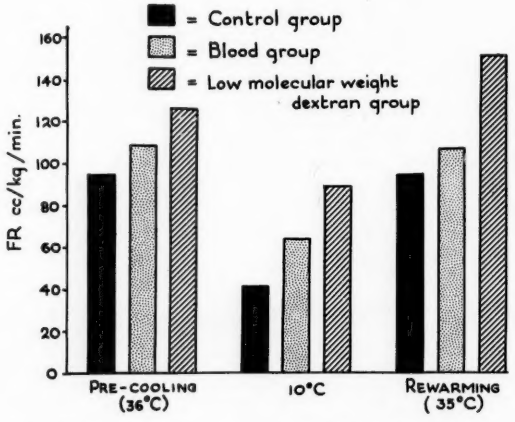

Fig. 3.—Average systemic flow rates during bypass of the three groups prior to cooling, at 10°C. and on rewarming.

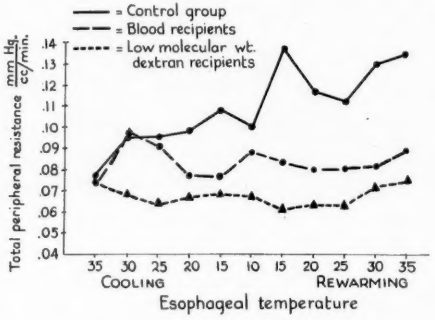

Fig. 4.—Average changes in total peripheral resistance of each group during perfusion.

b. *Total peripheral resistance:* Total peripheral resistance was calculated from the systemic flow rates and mean arterial pressure according to the formula—T.P.R. = BP/F.R. The results are shown in Fig. 4. The LMWD group had the lowest average peripheral resistance throughout the bypass. The peripheral resistance of the control group increased during the bypass, as did that of the blood recipients.

c. *Arterial and venous pressures:* The mean arterial pressure changes reflected in general changes of the systemic flow rate. The average pressure was slightly higher in the LMWD group but not significantly so. Immediately after the initiation of the bypass, the pressure usually fell by 20 to 40 mm. Hg but

promptly rose again. After this, it fell gradually throughout cooling to a level of 40 to 60 mm. Hg. During rewarming, the pressure rapidly returned to normal.

The venous pressure was an index of the adequacy of right atrial drainage and remained below 10 cm. H_2O in all three groups.

2. *Temperature Changes.*—

a. *Esophageal:* These are shown in Fig. 5 and Table I. Cooling and rewarming rates were highest in the LMWD group and of intermediate value in the blood group. The animals in the control and blood groups could not all be cooled to 10° C.; therefore, average temperatures of slightly above 10° C. were recorded for these two groups. The difference in cooling time between the control and LMWD groups was significant ($p = 0.0005$), as was the difference between the LMWD group and the blood group ($p = 0.0008$).

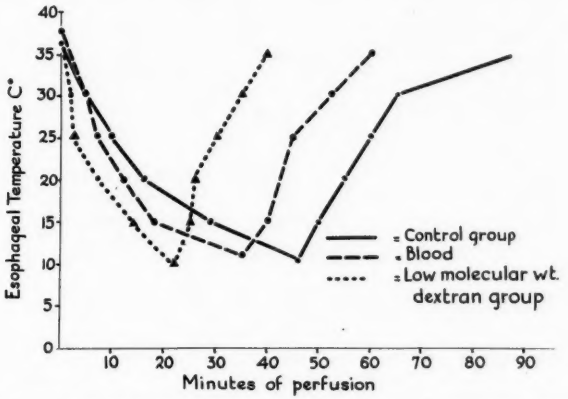

Fig. 5.—The average changes during bypass in the esophageal temperature of the three groups during cooling and rewarming.

TABLE I. THE CALCULATED AVERAGE COOLING AND REWARMING RATE OF EACH GROUP

	CONTROL (PER MIN.)	BLOOD (PER MIN.)	LMWD (PER MIN.)
Esophageal temperature			
Cooling	0.77° C.	0.81° C.	1.41° C.
Warming	0.77° C.	0.93° C.	1.35° C.
Muscle temperature			
Cooling	0.36° C.	0.29° C.	1.0° C.
Warming	0.16° C.	0.13° C.	0.62° C.

b. *Muscle:* As shown in Fig. 6, muscle temperature changes lagged behind those of the esophagus. This has been frequently described previously. The LMWD animals had the greatest average fall in muscle temperature. The difference in muscle temperature was significant for the LMWD and blood groups ($p = 0.0001$) and the control and blood groups ($p = 0.01$). During rewarming, the muscle temperature rose slowly and was usually below 30° C. by the end of the end of the bypass.

c. *Cardiac:* The cardiac temperature fell to an average of 11° to 14° C. in all groups. The cardiac rate rapidly declined with the onset of cooling and cardiac arrest, arbitrarily defined as less than two beats per minute, occurred between 15° and 20° C. No fibrillation occurred during cooling. It was noted, however, in about half the animals during rewarming between 18° to 30° C. All were defibrillated successfully by the application of electric shock.

3. *Hematologic Findings.—*

There was no significant difference in the findings of the three groups; therefore, these are reported together.

a. The plasma hemoglobin level rose during the bypass and averaged 56 mg. per cent higher than the precooling value.

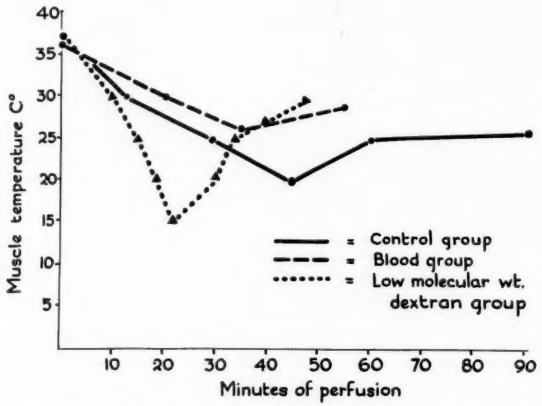

Fig. 6.—The average changes during bypass in muscle temperature of each group during the cooling and rewarming periods.

b. A drop in the hematocrit by 10 points or more, frequently occurred during the cooling period. The average hematocrit fell from 43 per cent to 33 per cent. After rewarming it was 37 per cent.

c. The average pH rose from a precooling value of 7.5 to 7.65 during cooling. Following rewarming it was 7.35.

d. Arterial oxygen saturation remained near 90 per cent during the bypass. The venous oxygen saturation was near 75 per cent during cooling and fell to 57 per cent by the end of rewarming.

4. *Survival.—*

Barring seven technical deaths, all animals survived the operation. Of the animals which received blood prior to the bypass, 3 were dead within 24 hours. In the other two groups there were four deaths attributable to abnormalities not directly related to the bypass. Of the remaining animals in which survival was expected, 60 per cent of the control group and 80 per cent of the LMWD group survived for 2 weeks or more. Postoperative shock unresponsive to blood or pressor drug administration was the most frequent cause of death. The difference in survival rate was not statistically significant.

DISCUSSION

The rapid induction of hypothermia in cardiac surgery requires a blood cooler providing outflow temperatures just above freezing and a high systemic flow rate. If a period of total circulatory arrest is to be used, cooling in various parts of the body should be uniform.

Low molecular weight dextran appears to be useful both in maintaining a high systemic flow rate during direct blood cooling and in reducing the magnitude of differential temperature levels.

These effects are partly due to an increase in the plasma osmotic pressure,[15] which results in a greater plasma volume. The latter is known to be reduced during hypothermia[6, 13] but can be restored to normal by the administration of LMWD. Plasma or saline, on the other hand, has little or no effect.

The low peripheral resistance observed in the LMWD animals is probably also important in the maintenance of a high systemic flow rate during perfusion. We initially thought that LMWD decreased blood viscosity, which would account for the low peripheral resistance; measurements with conventional viscosimeters have not confirmed this view. Such viscosimeters are intended for homogeneous fluids, however, and are probably not satisfactory for measuring blood viscosity.

Gelin and Lofstrom have reported that intravascular aggregation of the blood of hypothermic animals can be prevented by the administration of LMWD.[10, 12] They state that blood "sludging" results in pooling of the blood in the capillary bed, increased blood viscosity and increased peripheral resistance.

Our own results show that LMWD increases systemic blood flow during cooling and maintains a low peripheral resistance. The blood flow to muscle seems to be increased. We conclude that small quantities of low molecular weight dextran can be used during extracorporeal circulation to provide faster induction of hypothermia with more uniform cooling.

SUMMARY

1. The effect of low molecular weight dextran on the systemic flow rate during autogenous oxygenation with direct blood cooling has been studied in 52 dogs cooled to 10° C. Twenty-eight of these animals received 10 to 12.5 c.c. per kilogram of LMWD just prior to the bypass. Five of these received 12.5 c.c. per kilogram of whole blood before the bypass. Nineteen animals served as controls and received neither blood nor colloid.

2. The average systemic flow rate prior to cooling was 95, 109, and 126 c.c. per kilogram per minute for the control, blood, and LMWD groups, respectively. With cooling these values fell to 41, 64, and 88 c.c. per kilogram per minute; with rewarming they rose to 95, 107, and 153 c.c. per kilogram per minute.

3. The total peripheral resistance increased progressively throughout the bypass in the control group and blood recipients. The LMWD group, however, had a low total peripheral resistance which did not rise during perfusion.

4. Esophageal cooling rates of 0.77° C. per minute were obtained for the control group. Rates of 0.81 and 1.41° C. per minute were obtained for the blood and LMWD group, respectively. Rewarming rates were somewhat lower. The cooling rate for muscle was 1.0° C. per minute in the LMWD group. It was 0.29° and 0.36° C. per minute in the blood and control groups, respectively.

5. The survival rate was 60 per cent in the control group, 40 per cent in the blood group, and 80 per cent in the LMWD group.

6. We believe that LMWD may be used clinically in extracorporeal circulation employing direct blood cooling since it appears to increase systemic flow rate and provide faster, more uniform, cooling and rewarming.

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(For Discussion, see page 779)

MECHANISMS OF PULMONARY HYPERTENSION IN ACUTE HYPOXIA

Ibrahim K. Dagher, M.D. (by invitation), Henry G. Mishalany, M.D. (by invitation), and Fiorindo A. Simeone, M.D. (by invitation), Beirut, Lebanon
Sponsored by John L. Wilson, M.D.

PREVIOUS workers have demonstrated the occurrence of pulmonary arterial hypertension in hypoxia.[1, 2] Some authors have ascribed this hypertension to the local action of the hypoxic gases in the alveoli.[3] Others, utilizing a 99.5 per cent nitrogen and 0.5 per cent oxygen mixture, have related it to the inability of the hypoxic left heart to drain adequately the pulmonary veins, resulting in a retrograde rise in the pulmonary arterial pressure.[2] Still others blame this rise on a reflex pulmonary vasoconstriction.[1, 4] Stroud and Rahn[7] demonstrated an increase in the pulmonary vascular resistance under hypoxia in the intact animal; this increase did not occur in the sympathectomized animals. Nahas and his associates[6] demonstrated that thoracic sympathectomy in dogs did not completely eliminate the hypertensive response in the pulmonary circuit during hypoxia.

From this brief review of the literature it is evident that the mechanisms of the production of pulmonary hypertension in hypoxia are not well understood. It is the purpose of this paper to consider the possible mechanisms of the production of pulmonary hypertension under acute hypoxia. The role of the vagus, the glossopharyngeal, and the thoracic sympathetic nerves, the adrenal glands, the effect of the right ventricular output, left heart failure, and the action of phentolamine (Regitine) have been studied.

MATERIAL AND METHODS

Forty adult mongrel dogs, weighing between 15 and 22 kilograms each, were divided into 10 groups. The animals were anesthetized with the intravenous administration of 25 mg. of Pentothal sodium per kilogram of body weight. Each had a cuffed orotracheal tube and was given artificial respiration with an automatic respirator in a closed circuit with a CO_2 absorber. Bilateral thoracotomy was performed and, after full heparinization of the animal with the intravenous injection of 2.5 mg. of heparin per kilogram of body weight, the right femoral artery was cannulated and its pressure was measured with a mercury manometer.

From the Surgical Research Laboratory, American University of Beirut, Beirut, Lebanon.
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The femoral vein was cannulated as well as a segmental pulmonary artery and vein, and their pressures were recorded at one minute intervals with water manometers. In the group of animals in which pulmonary vein congestion had to be prevented, the appendage of the left auricle was incised and cannulated and decompressed by shunting part of its blood content into the right femoral artery with a Sigmamotor pump, keeping the pulmonary vein pressure at or around control levels.

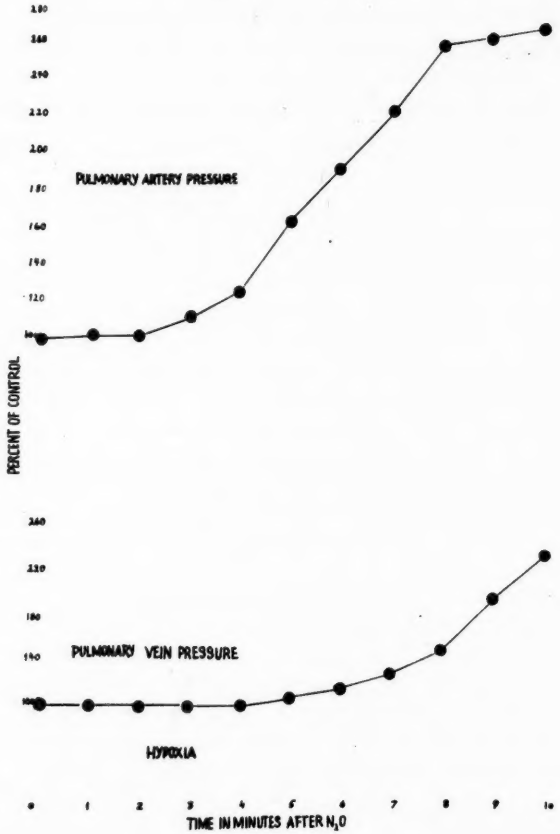

Fig. 1.

In the group of animals in which the right ventricular output was to remain constant, the venae cavae were cannulated and their total venous return was pumped with a Sigmamotor pump at a constant flow rate into the right auricle. The thoracic sympathetic, the vagi, and the glossopharyngeal nerves were stimulated with silver wire electrodes connected to a Grass Model 3C stimulator, using a monophasic current, 9 volts, an amplitude of 10 and a frequency F. Bilateral total adrenalectomy was done through a midline abdominal incision. Nitrous oxide was chosen as the hypoxic agent because the circulatory changes it induces are known to be due to hypoxia.[5] The experiments were carried out for an average duration of 10 minutes at which time the heart would dilate and go into asystole.

THE EXPERIMENTAL GROUPS

In the 10 different groups of animals the different experiments are conducted as follows:

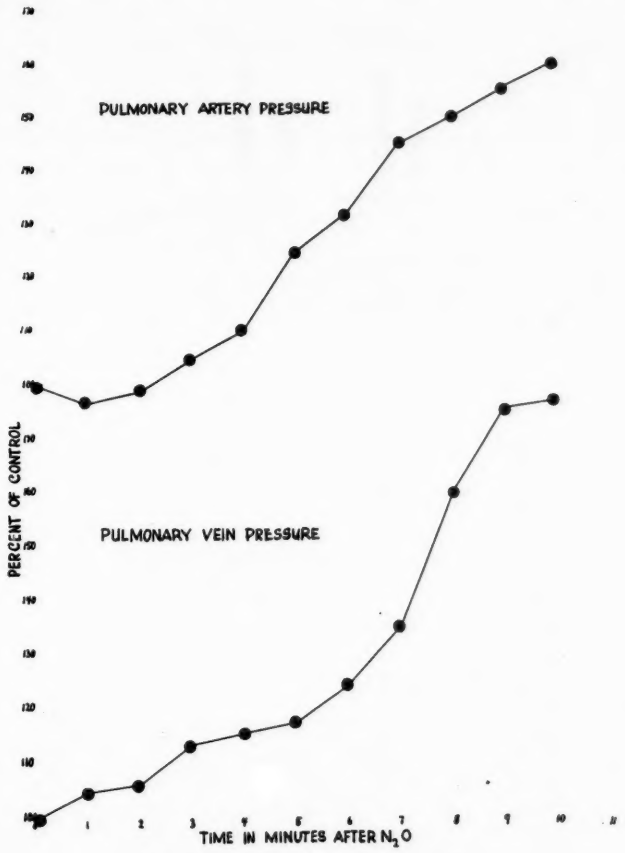

Fig. 2.—Hypoxia with sympathectomy.

Group I.—The control group.

Ten animals were prepared as described and were left undisturbed to breath room air with the help of a Starling's respirator. During this time the pulmonary artery and vein pressures were recorded and considered as base line control values. The animals were then made hypoxic and their pulmonary artery and vein pressures were recorded.

Results: After 10 minutes of nitrous oxide administration the pulmonary artery pressure rose to 270 per cent of its control level. The pulmonary artery pressure rose three minutes earlier than that of the pulmonary vein (Fig. 1).

Group II.—The sympathectomy group.

Four animals were prepared and subjected to hypoxia after bilateral thoracic sympathetic ganglionectomy with removal of all sympathetic ganglia and nerves, starting with the stellate ganglion down to the level of the diaphragm.

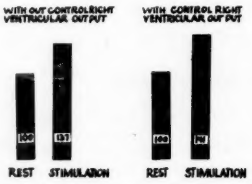

Fig. 3—Bilateral electrical stimulation of thoracic sympathetic nerves.

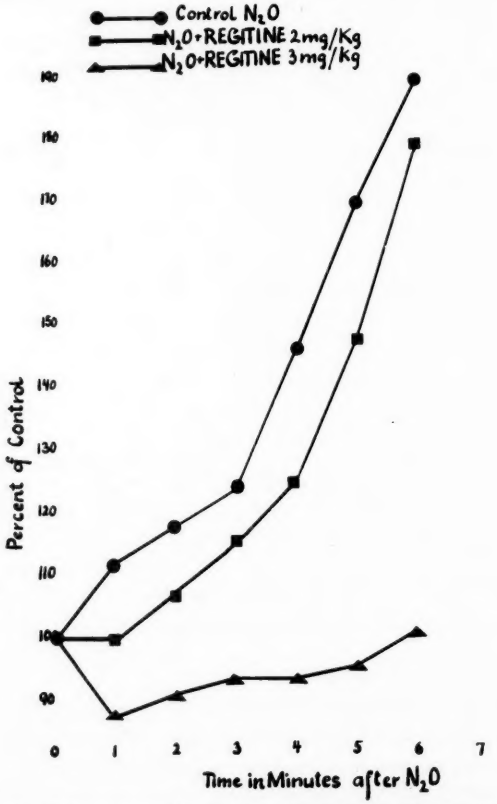

Fig. 4.—Pulmonary artery pressure in hypoxia with Regitine.

Results: The rise in the pulmonary artery and pulmonary vein pressures were concomitant but unequal. In this experiment, however, the rise in the pulmonary artery pressure reached only 160 per cent of the control (Fig. 2).

Group III.—The sympathetic stimulation group.

In 2 animals, the thoracic sympathetic chains were simultaneously stimulated just below the stellate ganglion and pressures were recorded. The same type of a stimulus was carried in face of a constant right ventricular output as indicated under Group IX.

Results: Direct bilateral electrical stimulation of the sympathetic nerves induced a rise of 137 per cent in the pulmonary artery pressure. The rise in the pulmonary artery pressure was about of the same magnitude (141 per cent) when the sympathetic stimulation was coupled with a controlled right ventricular output (Fig. 3).

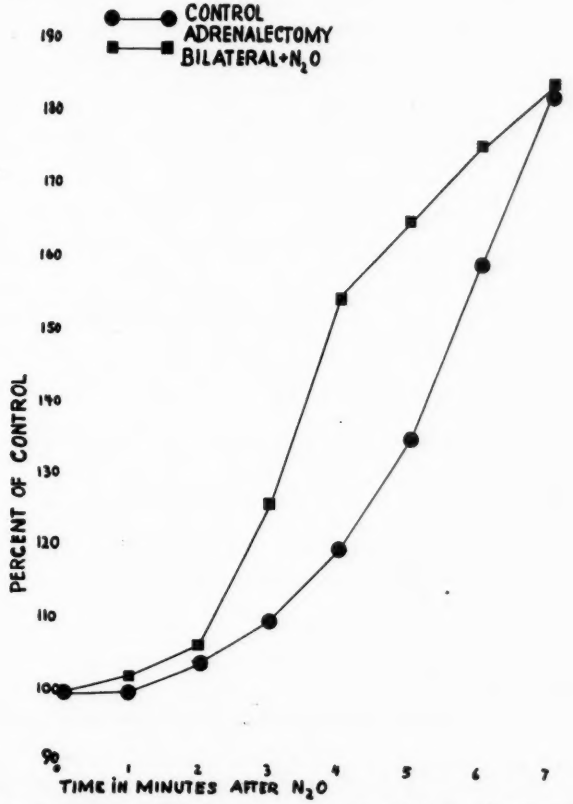

Fig. 5.—Pulmonary artery pressure in hypoxia, bilateral adrenalectomy.

Group IV.—The phentolamine (Regitine) group.

In this group of 4 animals, after a control hypoxia curve had been obtained, resuscitation was carried out by the inhalation of oxygen. Regitine was then given intravenously in doses varying between 1 and 2 mg. per kilogram of body weight, following which nitrous oxide was administered and pressures were

recorded for 7 consecutive minutes. Again the animal was resuscitated with oxygen and a second dose of Regitine, varying between 3 and 4 mg. per kilogram of body weight, was administered, and pressures were recorded after reinduction of hypoxia.

Results: The rise in the pulmonary artery pressure occasioned by hypoxia was reduced by the sympatholytic action of phentolamine (Regitine). This

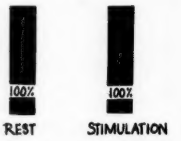

Fig. 6.—Electrical stimulation of the cervical vagi.

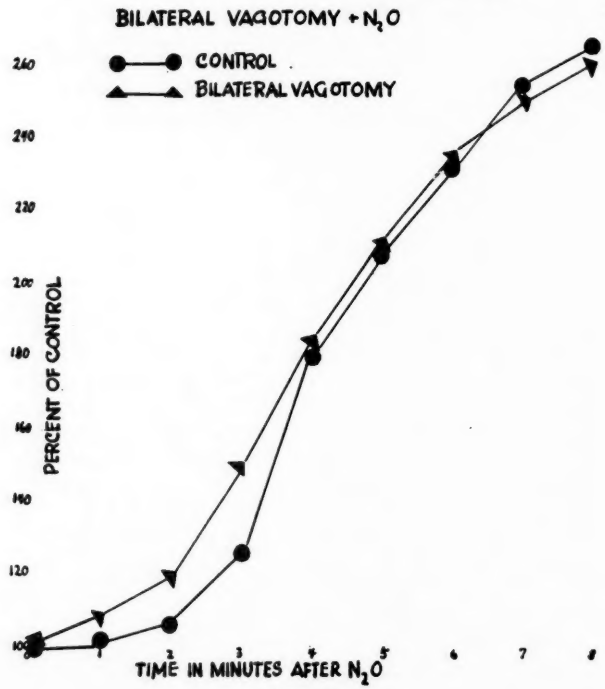

Fig. 7.

reduction was proportional to the amount of Regitine used and varied in the different animals. When an effective dose was used no rise in the pulmonary artery pressure was observed prior to the onset of left heart failure (Fig. 4).

Group V.—The adrenalectomy group.

In 2 dogs, a hypoxia control curve was obtained. The dogs were then given oxygen and subjected to a bilateral adrenalectomy using a midline abdominal incision. Nitrous oxide was administered and pressures were recorded.

Results: Following bilateral total adrenalectomy, the rise in the pulmonary artery pressure during hypoxia was identical with that observed in the control group (Fig. 5).

Group VI.—The vagotomy group.

In 2 animals, the cervical vagi were simultaneously electrically stimulated and pressures were recorded (Fig. 6). Then a control hypoxia curve was obtained and the animals were resuscitated with oxygen and subjected to a bilateral cervical vagotomy and pressures were recorded after the reinduction of hypoxia.

Results: Electrical stimulation of both cervical vagi does not affect the pulmonary artery pressure (Fig. 6). After bilateral cervical vagotomy, the rise in the pulmonary artery pressure induced by hypoxia was identical to that observed in the control experiments (Fig. 7).

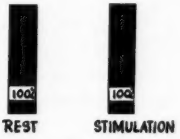

Fig. 8.—Bilateral electrical stimulation of the glossopharyngeal nerves.

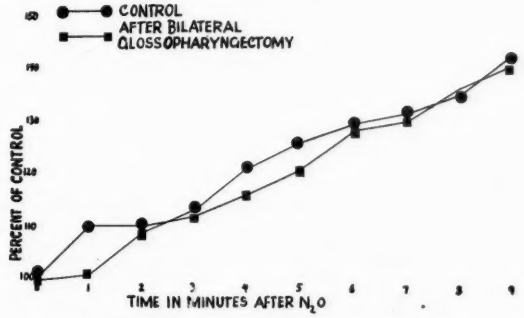

Fig. 9.—Glossopharyngectomy with hypoxia.

Group VII.—The glossopharyngeal nerve section group.

In 2 animals, the same experimental steps were carried out on the glossopharyngeal nerves as already described for the vagi under Group VI.

Results: Electrical stimulation of both glossopharyngeal nerves at their exit from the skull did not affect the pulmonary artery pressure (Fig. 8). After bilateral glossopharyngeal nerve section, the rise in the pulmonary artery pressure induced by hypoxia was identical with that observed in the control experiments (Fig. 9).

Group VIII.—The left auriculo-femoral artery shunt group.

In 2 animals, blood was shunted from the left auricle to the left femoral artery through the use of a Sigmamotor pump. The volume of this shunt was

regulated so as to keep the pulmonary vein pressure at or around base line control level.

Results: The pulmonary artery pressure rose shortly after the induction of hypoxia and reached 210 per cent of the control in 10 minutes. The prevention of pulmonary venous congestion markedly reduced the rise in the pulmonary artery pressure during hypoxia (Fig. 10).

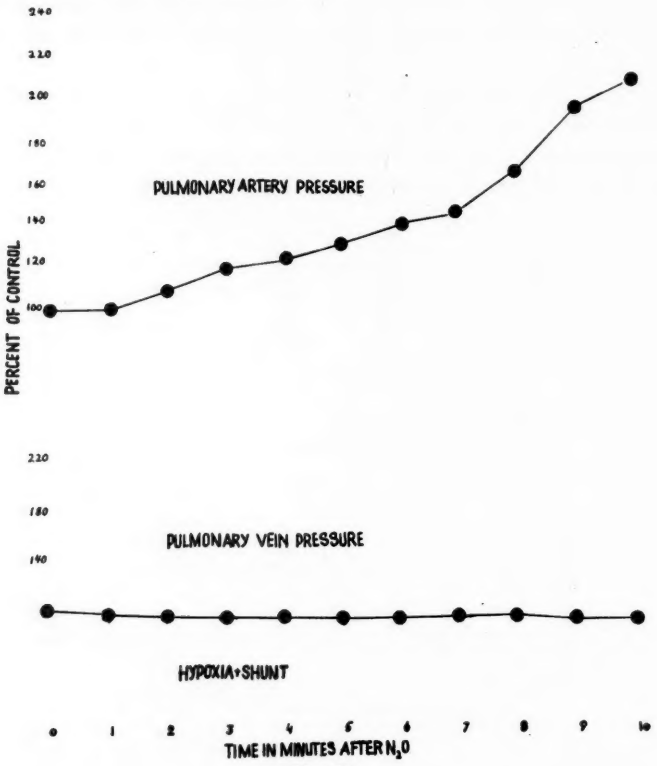

Fig. 10.

Group IX.—The constant right ventricular output group.

In 2 dogs, the right ventricular output was kept constant by the use of a Sigmamotor pump which delivered to the right auricle the blood of the cannulated venae cavae. The volume of the shunt was regulated before hypoxia so as to keep the systemic venous pressure around the control base line level. Thereafter hypoxia was induced and the shunt was left undisturbed. Pressures were recorded.

Results: When the blood delivered to the right ventricle was constantly kept around its base line value, keeping the systemic venous pressure at control level, the rise in the pulmonary artery pressure during hypoxia was similar to that observed in the control group (Fig. 11).

Group X.—The sympathectomy and left auriculo-femoral artery shunt.

In this group of 8 animals, bilateral thoracic sympathetic ganglionectomy was coupled with left auriculo-femoral artery shunt as described under Groups III and VIII. Nitrous oxide was then administered and pressures were recorded.

Results: When bilateral thoracic sympathectomy was coupled with a left auriculo-femoral artery shunt, no rise in the pulmonary artery pressure was observed during hypoxia (Fig. 12).

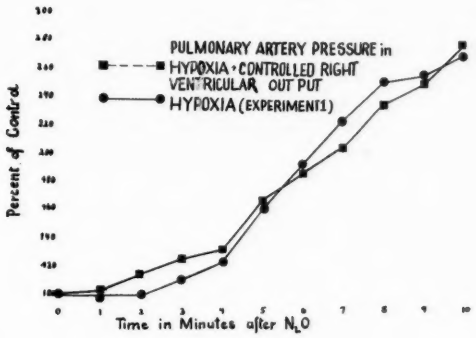

Fig. 11.

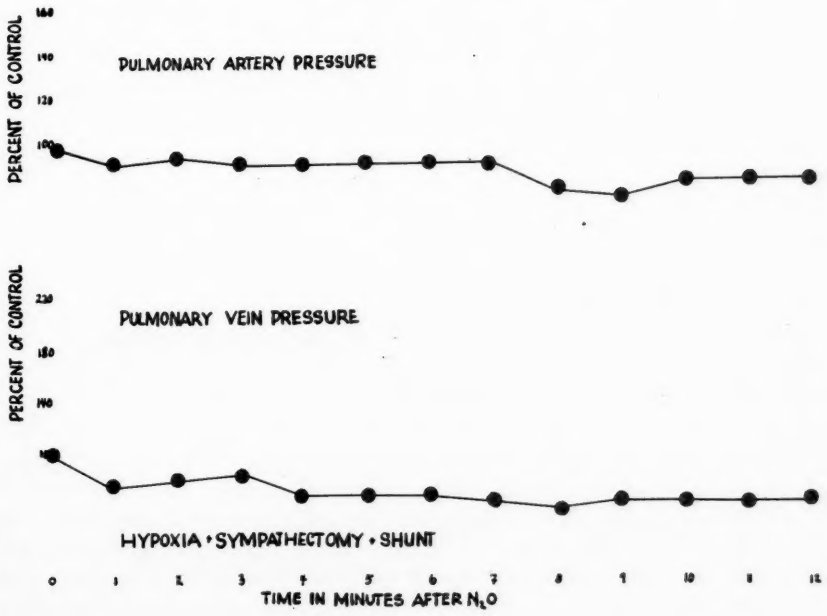

Fig. 12.

DISCUSSION

The pulmonary arterial hypertension induced by the inhalation of nitrous oxide can be explained by either one or a combination of the following mechanisms: (1) reflex pulmonary vasoconstriction originating in the carotid body or aortic arch, (2) hormonal mechanisms, (3) increased right ventricular output, (4) left heart failure, (5) anoxia to the central nervous system causing vaso-

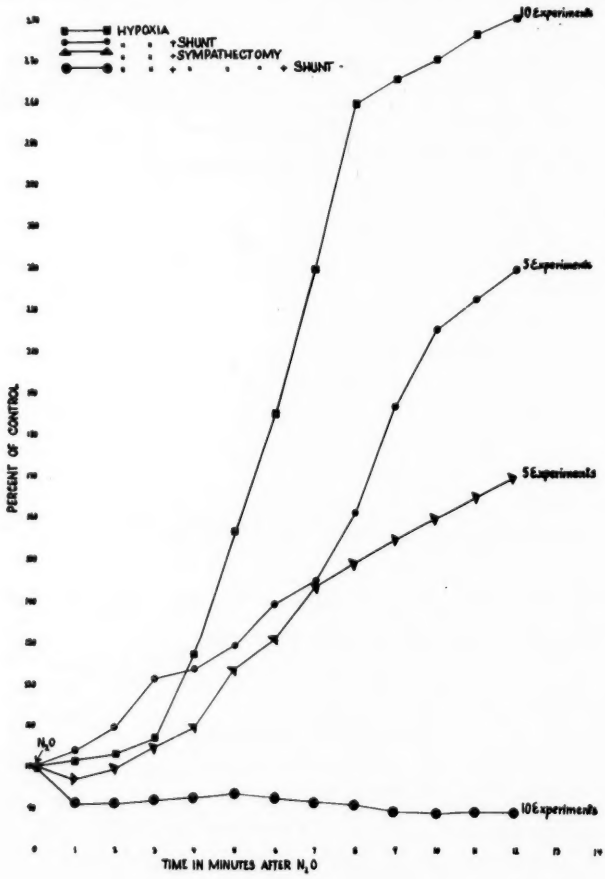

Fig. 13.

constriction through the thoracic sympathetic system, and (6) direct vasoconstriction of the hypoxia on the pulmonary vasculature.

The receptor cells in the carotid bodies and the arch of the aorta relay their impulses to the central nervous system through the glossopharyngeal nerves and the vagus nerves, respectively. During the control period the electrical stimulation of these nerves does not raise the pulmonary artery pressure. Conversely,

their ablation neither prevents nor does it decrease the pulmonary arterial hypertension during hypoxia. This is ample evidence that neither the carotid bodies nor the aortic arch have any demonstrable role in the production of pulmonary hypertension in acute hypoxia.

The adrenal glands do not seem to play a role in the production of pulmonary hypertension during acute hypoxia. This is evident from the fact that bilateral adrenalectomy did not alter the pulmonary hypertensive response to acute hypoxia.

Theoretically, when the right ventricular output increases beyond the ability of the pulmonary vessels to accommodate the increased flow, a rise in the pulmonary artery pressure is expected. It seems unlikely under the conditions of the experiment that the rise in the pulmonary artery pressure depends upon an increased right ventricular output. This is evident from the fact that, when the right ventricular output was kept constant and hypoxia was induced, the development of pulmonary artery hypertension was identical with that of the control group.

Failure of the left side of the heart, indicated by a rise in the pulmonary venous pressure, intensifies the arterial pulmonary hypertensive response to hypoxia. Conversely, the prevention of left heart failure by the use of the left auriculo-femoral artery shunt results in a decrease in the magnitude of the pulmonary arterial hypertension from 270 to 210 per cent.

These findings are in agreement with those of previous workers in demonstrating the role that left heart failure plays in the development of pulmonary arterial hypertension in hypoxia. Left heart failure, however, is not the only operating factor since, before its onset and in spite of its prevention, there is a marked rise in the pulmonary artery pressure. This rise is accounted for by the stimulation of the thoracic sympathetic system. The electrical stimulation of the thoracic sympathetic nerves resulted in pulmonary hypertension during the control period. After bilateral thoracic sympathectomy, pulmonary hypertension was evident only after the rise in the pulmonary vein pressure had reached 160 per cent of the control level.

This is ample evidence that the two main factors which produce pulmonary hypertension are sympathetic stimulation and left heart failure. As a matter of fact, when both of these factors were simultaneously eliminated, the first by thoracic sympathectomy and the second by left auriculo-femoral artery shunt, the pulmonary artery pressure did not rise above its base line control level and remained at this level until complete cardiac standstill. These findings also eliminate other factors, such as, hormones and direct action of hypoxia on the pulmonary vasculature, as possible mechanisms in pulmonary hypertension in acute hypoxia. The relative merits of the sympathetic system and of the failure of the left heart in the development of pulmonary hypertension in acute hypoxia are demonstrated by comparing the rise in the pulmonary artery pressure in sympathectomized animals and in face of a decompressed left auricle with the control group (Fig. 13).

CONCLUSION

From the above experiments, it is submitted that during acute severe hypoxia: (a) there is a rise in the pulmonary artery pressure, (b) this rise is initiated and maintained by the thoracic sympathetic nerves from stimuli originating in the central nervous system, (c) the left heart failure that sets in during the latter course of the experiment adds to the intensity of the pulmonary hypertension, and (d) there is no other demonstrable mechanism in play.

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(For Discussion, see page 779)

EXPERIENCES WITH NaI^{131} INJECTED INTO THE MYOCARDIUM AS AN ESTIMATE OF CORONARY BLOOD FLOW

Irving M. Madoff, M.D., and William Hollander, M.D. (by invitation), Boston, Mass.

THE quantitative determination of coronary blood flow in man has been accomplished repeatedly since 1949, when the nitrous oxide technique first used for measurement of cerebral blood flow[1] was adapted to this purpose.[2] The disadvantages of this method consist of the inability to detect rapid changes in coronary flow and in the occasional problems and time involved in catheterization of the coronary sinus required by the technique.[3] Nevertheless, much valuable information has been obtained with this method concerning coronary blood flow in man, both in health and disease, and concerning the influence of various pharmacologic agents.[4]

With a view to simplification of technique and to the detection of rapid variations in coronary blood flow, methods utilizing radioactive isotopes for the determination of flow have been introduced. These consist of recording the passage of radioisotopes through the coronary circulation[5] or of recording the uptake of radioactive tracers, specifically Rubidium[86], by the heart muscle.[6] Previous studies in this laboratory indicate (1) that a tracer dose of NaI^{131}, when injected directly into a tissue, disappears in proportion to the arterial blood flow through the tissue, and (2) that a tracer dose of I^{131}-labeled albumin disappears in accordance with the integrity of the lymphatic system and that it is impeded by obstruction to this system.[7] The foregoing, together with the observations of Kety[8] and Walder[9] on limb tissue, suggested that NaI^{131}, when injected into the myocardium, might disappear from the injection site in accordance with coronary blood flow. This has been confirmed in our preliminary studies.[10] It is the purpose of this communication to report on the methods of study in the use of NaI^{131} injected into the myocardium in laboratory animals and in human subjects and to review our experiences with this technique.

METHODS

I. Healthy mongrel dogs were anesthetized by intravenous administration of pentobarbitol sodium. An endotracheal tube was inserted which was connected to a mechanical

From the Department of Surgery and the Department of Medicine, Boston University School of Medicine, and the Thoracic Surgical Service and the Medical Service, Massachusetts Memorial Hospitals, Boston, Mass.

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respirator as soon as the thorax was opened. A left thoracotomy was performed through the left fifth intercostal space and the pericardium was incised anterior to the left phrenic nerve. The left coronary artery and its major branches were identified and the proximal end of the anterior descending branch of the left coronary artery was mobilized. With the base of the scintillation detector placed approximately 3 inches above the heart, 2 to 4 μc of NaI^{131} in 0.2 ml. of solution was injected into the ventricular apex. The scintillation detector was attached to a rate-meter* and a recorder, and continuous recordings were made. The sodium iodide crystal of the detector was 1½ inches in diameter and 1 inch in thickness. A cylindrical collimator, with a diameter of 1½ inches, was fitted over the crystal.

Using a rubber-shod small Blalock-type clamp, the anterior descending branch of the left coronary artery was completely occluded. This resulted in a large area of cyanosis of the portion of the ventricle surrounding the artery. As soon as cyanosis was achieved, a tracer dose of NaI^{131} in 0.2 ml. of solution was injected into the cyanotic portion of the ventricular myocardium with the scintillation detector maintained in the same position as previously. Continuous recordings were made and, after 1 to 2 minutes, the clamp was released. With release of the clamp, cyanosis completely disappeared. Recordings were continued throughout the study.

Using the same method as above, total occlusion of the anterior descending branch of the left coronary artery was obtained and then the clamp was partially released. A tracer dose of NaI^{131} in the same volume was injected into the ventricular myocardium. After recording the radioactivity with partial occlusion, the clamp was removed and recording was continued.

II. During open thoracotomy for intrathoracic disease, the pericardium was incised and the myocardium was exposed. Five to ten microcuries in 0.5 ml. of solution was injected into the myocardium with the scintillation detector placed approximately 3 inches above the site of the injection. A recording of radioactivity was carried out until it disappeared.

III. *Percutaneous Injection of NaI^{131}.*—The patient lies supine with head elevated on a pillow in a comfortable position. The position of the apex beat is marked with indelible pencil. If this is not easily palpable, the position of the apex is determined by fluoroscopy and the skin is marked appropriately. An electrocardiograph is attached for continuous recording and blood pressure is monitored through the procedure. The patient is lightly premedicated with atropine and meperidine hydrochloride (Demerol). The entire anterior chest is prepared and draped with towels and sheets. The procedure of percutaneous myocardial puncture is carried out, in the manner described by Brock and associates,[11] for left ventricular puncture except that no attempt is made to enter the left ventricular chamber. The skin approximately 1 inch below the apex beat is infiltrated with 1 per cent procaine solution. The subcutaneous and intercostal tissue is also infiltrated with this local anesthetic agent. The anesthetic agent is not injected beyond the level of the intercostal tissue. A No. 22 gauge needle, 10 cm. long, contained a stylet is inserted into the site of anesthesia and is directed toward the right second costochondral junction with a backward inclination of approximately 30 degrees. As the myocardium is entered, ventricular motion can usually be palpated and there are always one or more extrasystoles seen on the electrocardiographic tracing which disappear spontaneously. Prior to the insertion of the needle, the scintillation detector is placed over the precordium slightly to the right of the position of insertion of the needle and a control tracing is made. The base of the detector is placed approximately 1 inch away from the skin. As soon as the needle has penetrated the ventricular myocardium, mild suction is applied to the needle through a syringe in order to make certain that no blood is obtained. If this occurs, the position of the needle is changed before continuing with the study. A solution of 5 to 10 μc of NaI^{131} and 0.5 ml. is now injected into the myocardium and the needle is immediately removed. The scintillation detector is maintained in the same position throughout the entire study. Electrocardiographic and blood pressure monitoring is continued through the study. A thoracotomy kit, an endotracheal tube, and

*Rate-meter, Model 432A, was obtained from Baird Atomic, Inc., Cambridge, Mass.

oxygen are available in the room for cardiac resuscitation. Following the procedure the patient is observed carefully with blood pressure, pulse, and respiration being recorded at frequent intervals. Chest roentgenograms were made immediately after completion of the study in the first few cases, but this has now been discontinued.

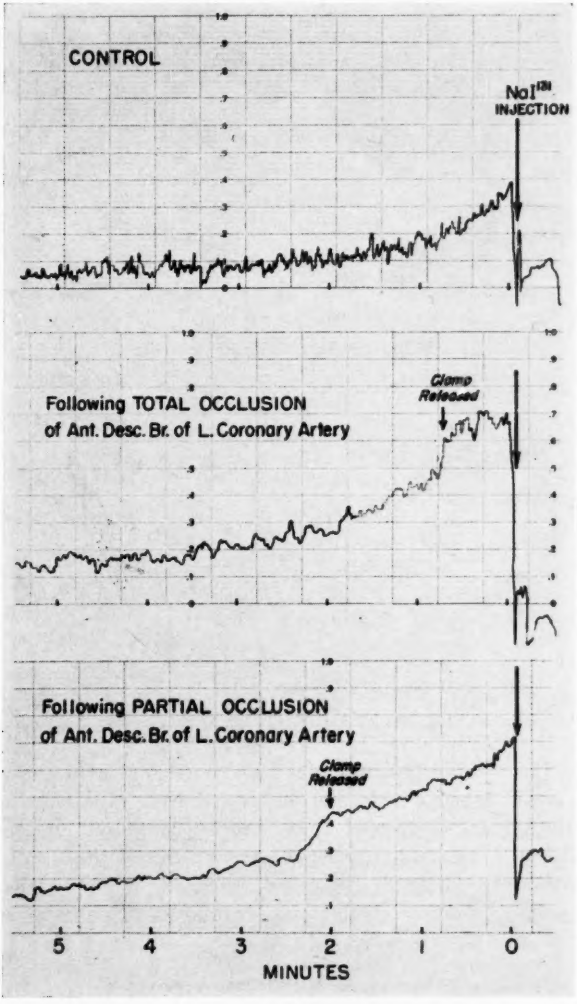

Fig. 1.—The disappearance of injected NaI^{131} from the myocardium of a dog.

RESULTS

I. In the control studies in the dog experiments, the NaI^{131} disappeared from the myocardium rapidly. A typical set of experiments on the removal of injected NaI^{131} from the myocardium of a dog is shown in Fig. 1.

In the upper and control tracing, NaI^{131} injected in the myocardium was removed rapidly and at an exponential rate, the half-time being about 1 minute. The latter portion of the curve represents background activity as revealed by external monitoring of other cardiac sites and by measurements of radioactivity in the blood.

With total occlusion of the anterior descending branch of the left coronary artery the NaI^{131} remained at the injection site until the clamp was released. With release of the coronary artery the NaI^{131} disappeared rapidly at approximately the same rate as in the control experiments (see middle tracing of Fig. 1).

Following partial occlusion of the anterior descending branch of the left coronary artery and the injection of NaI^{131} there was a slow disappearance of the injected material (see lower tracing, Fig. 1) until the artery was completely released by removal of the clamp. At this point, there was a rapid increase in the rate of removal of the NaI^{131} from the heart muscle. The irregularity seen in these curves is caused by the change in position of the injection site from the detector as a result of respiratory and cardiac movements. In a number of other studies these irregularities were reduced by prolonging the time constant of the rate-meter.

TABLE II. THE REMOVAL OF NaI^{131} FROM THE MYOCARDIUM OF PATIENTS DURING OPEN THORACOTOMY FOR INTRATHORACIC DISEASE

PATIENT	HALF-TIME (MIN.)	CORONARY ARTERY DISEASE
L. F.	1	No
L. F.	1½	No
G. D.	1	No
G. D.	1½	No
N. D.	1	No
D. V.	1¾	No
R. N.	1	No
L. T.	4½	Yes
L. T.	8	Yes
A. N.	10	Yes

II. (Table II.) In the patients who had no clinical evidence of coronary artery disease, NaI^{131} disappeared from the myocardium rapidly. In this group the half-time disappearance ranged from 1 to 1¾ minutes. In patients with documented clinical evidence of coronary artery disease, the disappearance of NaI^{131} was delayed. In patients L. F., G. D., and L. T., the injections were made into different areas of the ventricular myocardium at the time of thoracotomy (Fig. 2).

TABLE III. PERCUTANEOUS INJECTION OF NaI^{131} INTO THE VENTRICULAR MYOCARDIUM OF PATIENTS WITH CORONARY ARTERY DISEASE

PATIENT	T ½ IN MINUTES		
H. L.	10	12	13½
E. S.	1½	7½	
W. R.	2½	4	12
V. M.	1½	2	3
A. N.	4½	5	11
E. S.	¾	1½	

III. (Table III.) In this group of patients, separate injections were made on each patient and the disappearance rates are noted in Table III. In the patients with coronary artery disease the half-time disappearance of NaI^{131} ranged from 45 seconds to 13½ minutes, considering all patients, and averaged 5.8 minutes.

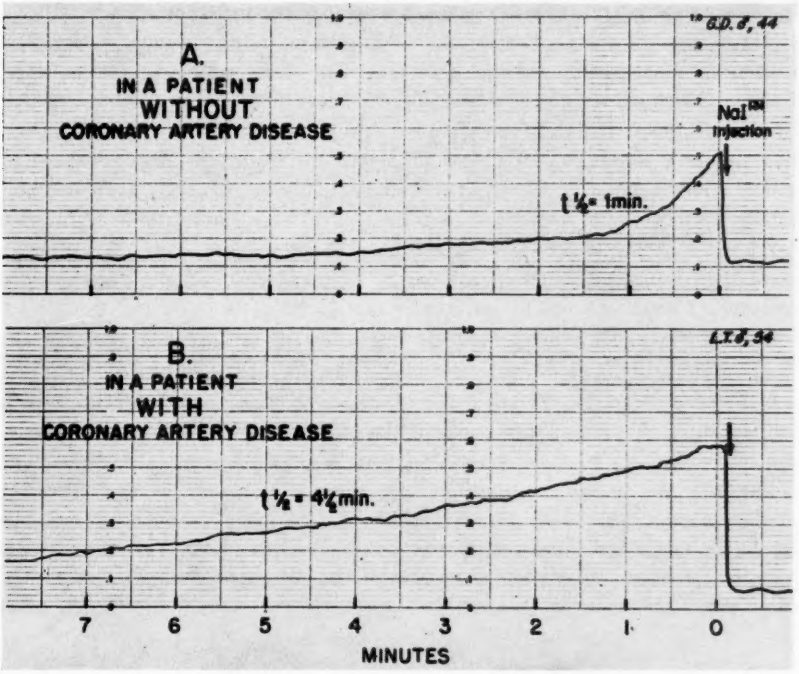

Fig. 2.—Tracings demonstrating the disappearance of NaI^{131} from the myocardium during open thoracotomy. *A*, A patient with no evidence of coronary artery disease. *B*, A patient with documented coronary artery disease.

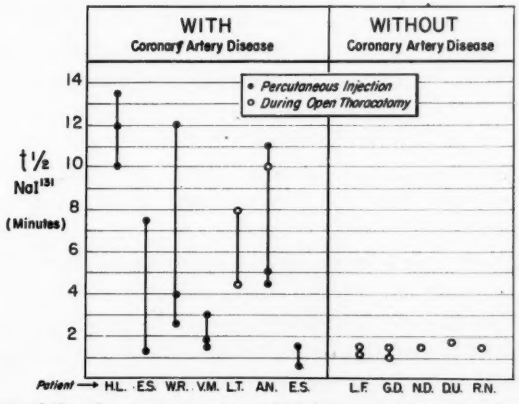

Fig. 3.—A summary of the disappearance rates of NaI^{131} from the myocardium in patients with and without coronary artery disease.

The rates of removal of NaI^{131} from the myocardium of 7 patients with, and 5 patients without, coronary artery disease are summarized in Fig. 3.

DISCUSSION

With the increasing attention during recent years to direct surgical attack on coronary vessels and with the development of operative techniques in atherosclerosis of the coronary arteries, the measurement of myocardial blood flow has assumed more than academic interest. The same problem obtains when one considers the multiple pharmacological agents becoming available which presumably improve coronary circulation. Coronary angiography is contributing significant data concerning the sites of abnormalities in the major vessels in coronary artery disease. However, the demonstration of apparently normal coronary angiograms in some patients with clinical arteriosclerotic heart disease and angina[12] serves to indicate that the total myocardial blood flow or the blood flow to an area of myocardium must be considered in attaining objective assessment of a patient or of any therapeutic regimen.

Bing and associates[3] have recently made a critical review of the current methods of measurement of coronary blood flow and have indicated the areas in which these methods are deficient. Kety[8] in 1949 reviewed previous work which indicated that when the tissue uptake of a substance is rendered measurable by the use of radioactive isotopes, it may be possible to measure blood flow without resorting to blood sampling. He pointed out that, if the diffusible tracer substances were introduced directly into a tissue instead of into the general circulation, the clearance from the tissue would depend upon the local tissue circulation and hence might represent a measure of the tissue circulation. He was able to make a mathematical analysis of the clearance of an injected substance from a tissue and injected the gastrocnemius muscle to study the validity of the proposition that clearance of a radioactive ion from a tissue offers a useful means for measurement of effective circulation in a particular tissue.

Hollander and associates[7] during a recent study of the measurement of the lymphatic flow in human subjects by the use of I^{131}-labeled albumin were able to demonstrate that the disappearance of NaI^{131} from the subcutaneous tissue is much more rapid than that of I^{131}-labeled albumin, that it is comparable in lymphadematous and in normal limbs, and that it is influenced by the degree of cardiac compensation. These findings were consistent with reports of others[8, 9] which indicated that the disappearance of inorganic ions from the tissues may be a useful index of blood flow. In the present study, previous observations,[8] in which Na^{24} remained at the injection site while the circulation to the gastrocnemius muscle was occluded and in which Na^{24} disappeared rapidly following release of a tourniquet, seem to be confirmed in our dog experiments with occlusion and release of the coronary artery and the measurement of radioactivity over the injected area of myocardium.

The rate of disappearance of NaI^{131} injected into the myocardium appears to be an index of myocardial blood flow in the local area. The variations in the rates of disappearance of NaI^{131} from the myocardium of patients with coronary artery disease appear to be related to a change in the site of injection and suggest variability in perfusion of different portions of the myocardium in these individuals. Further studies would seem to be necessary to establish the applicability of this method to the investigation of the possibility of selective perfusion in the normal myocardium.[13]

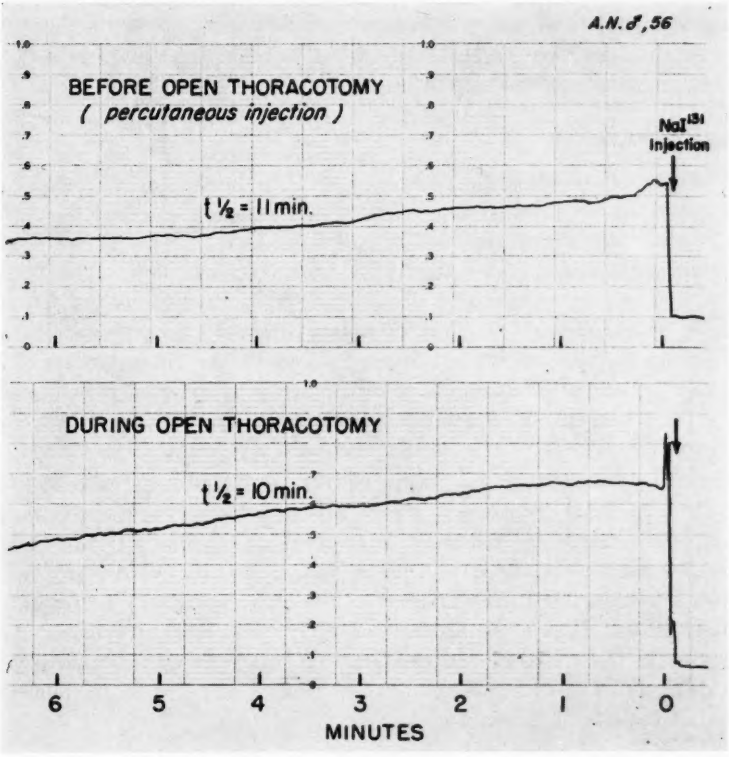

Fig. 4.—The disappearance of injected NaI^{131} from the myocardium of a patient with angina pectoris before and during open thoracotomy.

Our experience with the study of the disappearance of NaI^{131} from the myocardium of patients both before thoracotomy by percutaneous injection and during thoractomy by direct injection of the myocardium indicates that the results are comparable. The removal of NaI^{131} from the myocardium of a patient with coronary artery disease and angina pectoris is shown in Fig. 4. The tracings obtained before and during thoracotomy were similar. By percutaneous injection of NaI^{131}, the half-time was 11 minutes; at the time of operation, direct injection of the myocardium showed a half-time of 10 minutes.

The operation in this case consisted of a pericardial poudrage. The impaired removal of NaI^{131} from the ventricular apex was seen at operation to be associated with patchy fibrosis of the myocardium and with sclerosis of the coronary vessels.

The precedent for injection of the human myocardium under basal conditions without general anesthesia has been well established by frequent usage in one current technique of left heart catheterization[11] and by the more recent experiences of Sutton and Sutton[14] in obtaining biopsies of the ventriclar myocardium. In the present study, although all patients who received percutaneous injections of NaI^{131} had documented evidence of coronary artery disease and although each patient received two or more injections, no serious untoward incidents occurred during or after the procedure.

SUMMARY

Previous studies have been reviewed which indicate that the rate of disappearance of an ion injected into a tissue is a function of blood flow. In the present study, the rate of removal of NaI^{131} injected into the myocardium was observed in relation to the integrity of coronary blood flow. The procedure was carried out on anesthetized dogs during open thoractomy and on human subjects, with and without coronary artery disease, either percutaneously or during open thoracotomy for intrathoracic disease. The disappearance of NaI^{131} from the heart musele was measured continuously by externally monitoring the site of injection using a scintillation detector and appropriate recording instruments.

In anesthetized dogs the disappearance of NaI^{131} was extremely rapid. The rate of removal decreased as a coronary artery was progressively narrowed and stopped completely following total occlusion of the artery. In human subjects without coronary artery disease the disappearance of NaI^{131} was also rapid and comparable to the findings in the animal studies. In patients with coronary artery disease the removal of NaI^{131} was markedly impaired. The variations in the rates of disappearance of NaI^{131} from the myocardium of individual patients with coronary artery disease appears to be related to a change in the site of injection.

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(For Discussion, see page 779)

REPLACEMENT OF RIGHT VENTRICULAR MYOCARDIUM WITH A TEFLON PROSTHESIS

Harold A. Collins, M.D. (by invitation), J. Kenneth Jacobs, M.D. (by invitation), Robert T. Sessions, M.D. (by invitation), and Rollin A. Daniel, Jr., M.D., Nashville, Tenn.

REPLACEMENT of ventricular myocardium has potential value in the surgical management of several cardiac abnormalities. Despite the frequent use of prosthetic materials in cardiac surgery, they have rarely been used as a substitute for resected myocardium. The hemodynamic alterations resulting from the use of prosthetic materials in this manner are undetermined. If such replacements should prove practical it is possible that myocardial resection for infarction could be accomplished.

Murray[6] envisioned and applied, experimentally, resection of left ventricular myocardium following myocardial infarction. Ligation of the anterior descending coronary artery proximal to the two or three large terminal branches in dogs produces infarction of about 25 per cent of the left ventricular myocardium. The systemic blood pressure and cardiac output drop precipitously due to dilatation in paradoxical fashion of the infarcted myocardium. Resection of the infarcted myocardium and direct suture produces a striking increase in cardiac output and blood pressure. The extent of myocardial resection has been limited by the necessity for preservation of a minimal tolerable ventricular diastolic volume. Bailey and Gilman[1] demonstrated that a significant reduction in volume of the left ventricular cavity in dogs produced pulmonary edema, hepatomegaly, hydrothorax, and ascites. In addition, previous attempts at resection were limited by the method of applying large ventricular clamps for partial exclusion of the myocardium during excision and suture. Techniques for open-heart surgery and the development of satisfactory prosthetic materials for replacement have obviated these difficulties to a certain extent.

The present study was undertaken as a preliminary investigation concerning the feasibility of replacement of large portions of ventricular myocardium. The right ventricle, rather than the left, was selected for initial studies since the technical problems appeared less formidable and hemodynamic evaluation easier.

From the Department of Surgery, Vanderbilt Medical Center, Nashville, Tenn.

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METHODS

Unselected, adult, mongrel dogs, weighing from 12.8 to 21 kilograms, were used for all experiments. Anesthesia was induced and maintained by the administration of thiopental sodium intravenously. Pressures in the abdominal aorta and inferior vena cava were monitored throughout the experiment by use of pressure transducers and a direct writer recorder. Respirations were maintained by a respirator insufflating room air through a cuffed endotracheal tube. Under sterile conditions a right posterolateral thoracotomy through the fourth intercostal space was performed. Following the administration of heparin (2 mg. per kilogram), the superior and inferior venae cavae were intubated with large plastic catheters through the right atrium. Another catheter was inserted into the left atrium for decompression. Temporary cardiopulmonary bypass was accomplished by gravity venous drainage into a rotating disc oxygenator and return of oxygenated blood through a cannula in the femoral artery. Flow rates of 70 to 90 ml. per kilogram body weight per minute at normothermic temperatures were utilized. During myocardial resection and replacement, the ascending aorta was occluded intermittently to diminish coronary flow.

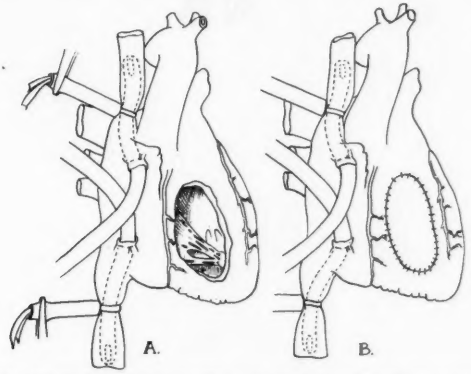

Fig. 1.—Diagrammatic illustration of resection of right ventricular myocardium and replacement with Teflon fabric during cardiopulmonary bypass.

Segments of the free right ventricular myocardium, varying in size from 2.5 by 5 cm. to 4 by 7 cm., were resected (Fig. 1). Teflon fabric of approximately equal size was sutured into the defect, utilizing a continuous over-and-over suture of fine silk. In 22 animals, a patch fashioned from a woven Teflon aortic graft* was utilized. Teflon felt ⅛ inch thick,* was used in 5 animals (Fig. 2). In 13 dogs, four or five right ventricular branches of the right coronary artery were ligated at their origin and resection of the infarcted portion of myocardium performed. Duration of cardiopulmonary bypass varied from 15 to 25 minutes. In the few animals in which ventricular fibrillation occurred, one to two shocks usually caused reversion. No attempt was made to close the pericardium. Polybrene was administered in a dose of 3 mg. per kilogram. After closure of the chest no special postoperative care was given except for evacuation of air and blood from the pleural space. All survivors were maintained for at least 6 weeks before sacrifice.

Cardiac output was determined by the dye dilution technique in most animals under sodium pentobarbital anesthesia preoperatively and 6 weeks postoperatively. Cardiac catheterization was performed in 6 animals at periods ranging from 2 to 4 months after operation. Animals were sacrificed periodically up to 6 months after operation for gross and microscopic observations of the heart. The cause of death was determined by autopsy examination in all animals that did not survive for 6 weeks.

*C. R. Bard, Inc., Summit, N. J.

RESULTS

Ten of 27 dogs survived for longer than 6 weeks (Table I). Most of the survivors appeared to be healthy, active animals. The most significant cause of death was necrosis at the ventricular suture line in 7 of 13 dogs in which myocardial infarction was produced. It was apparent that an insufficient resection of infarcted myocardium had been accomplished. Five of the seven

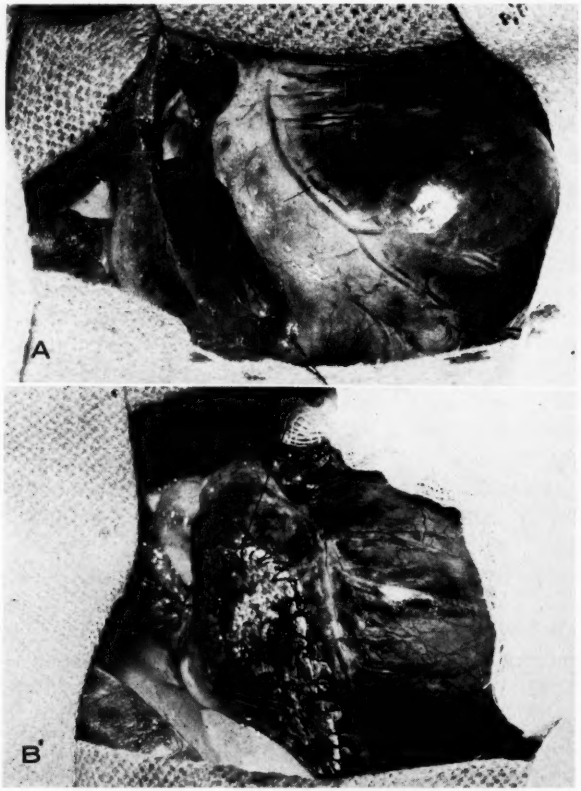

Fig. 2.—*A*, Operative photograph at right ventricular myocardial resection. Ventricular septum and pulmonary valve are visible.

B. Photograph at completion of replacement of right ventricular myocardium with Teflon felt. Blood oozing through the felt is apparent.

TABLE I. FATE OF ANIMALS FOLLOWING REPLACEMENT OF RIGHT VENTRICULAR MYOCARDIUM WITH A TEFLON PROSTHESIS

Survivors		10
Deaths		17
Rupture at graft site	7	
Pulmonary complications	7	
Unknown	2	
Anesthetic death	1	
		27

deaths in this group resulted from bleeding. In the other 2 animals the patch sloughed into the right ventricular cavity and produced partial obstruction with ascites and death at 5 and 6 weeks. Pulmonary complications caused seven deaths which could have been prevented by more arduous postoperative care. The cause of death in 2 dogs could not be determined. Anesthesia during a determination of cardiac output 6 weeks postoperatively caused death in one dog.

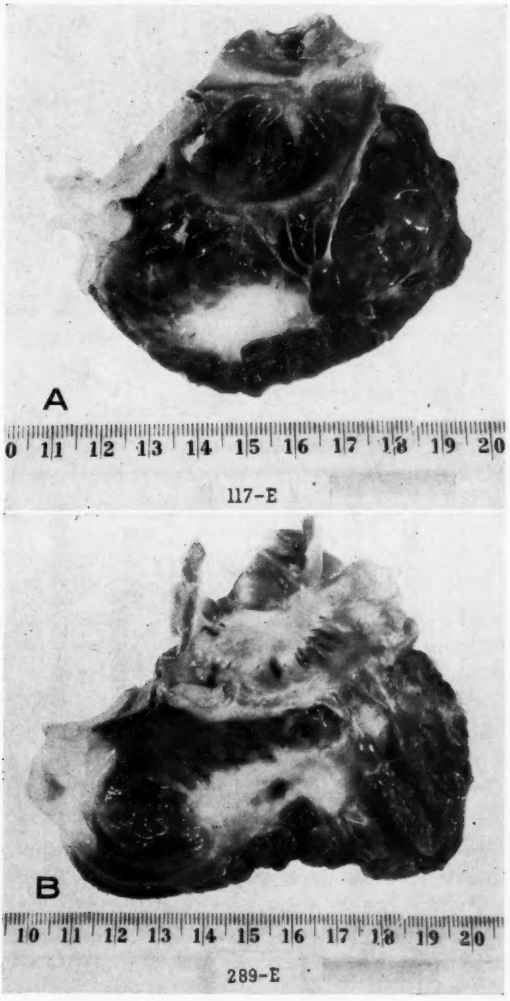

Fig. 3.—*A*, Opened right atrium and ventricle 2 months after replacement of right ventricular myocardium with woven Teflon prosthesis. Teflon patch completely covered by smooth glistening fibrous tissue.

B, Appearance of Teflon patch 5 months after operation. Fibrous tissue is thicker and patch appears smaller than it did at operation.

Nine of the 10 survivors were sacrificed at periods from 6 weeks to 6 months postoperatively. One animal is still alive 7 months after operation. Examination after sacrifice demonstrated the Teflon fabric to be well incorporated into the myocardium with no essential difference in the woven or felt fabric (Fig. 3). In most instances the lung was densely adherent to the external surface. The intraventricular surface of the fabric was covered with smooth

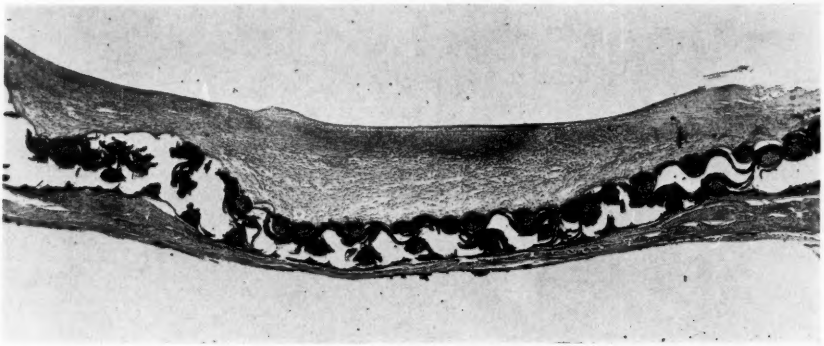

Fig. 4.—Microscopic appearance of Teflon graft 2 months postoperatively. Endocardial surface is at the top of the illustration.

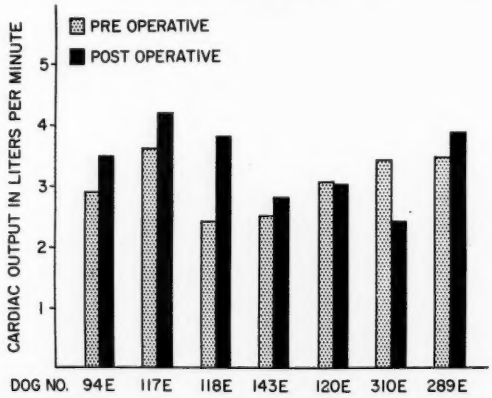

Fig. 5.—Graph of cardiac outputs determined by dye dilution technique before and 6 weeks after replacement of right ventricular myocardium with a Teflon prosthesis.

and glistening tissue. No thrombi were present. In no instance was embolization from or infection in or about a graft detected. In some specimens the patch appeared considerably smaller on the internal surface, particularly in the transverse diameter. It appeared that ventricular muscle had extended beneath the patch. Microscopic examination disclosed a relatively smooth and uniform layer of fibrous tissue on both sides of the Teflon with no evidence of degeneration (Fig. 4). Ingrowth of tissue through the fabric was not apparent. In several instances, foci of inflammatory cells were noted about the silk sutures.

Hemodynamic observation demonstrated little significant effect from resection of right ventricular myocardium and replacement with Teflon fabric. Systemic arterial and venous pressures were essentially the same preoperatively and postoperatively. Cardiac catheterization revealed normal pressures throughout the right side of the heart (Table II). The pulmonary arterial pressure pulse was normal in contour. Preoperative and postoperative estimation of cardiac output by the dye dilution technique revealed no significant changes (Fig. 5). Variations which did occur were well within the limits of error for determination of cardiac output by this method.

TABLE II. TYPICAL FINDINGS DETERMINED BY CARDIAC CATHETERIZATION IN DOG 2 MONTHS AFTER OPERATION

SITE	PRESSURE (MM. Hg)
Superior vena cava	6
Inferior vena cava	5
Right atrium	0–5
Right ventricle	35/0
Main pulmonary artery	36/10

DISCUSSION

Evidence obtained from our studies and those of others suggests that it is possible to inactivate, alter, or resect large portions of the right ventricular myocardium without adverse circulatory effects. Ernst and his associates[5] found that artificial enlargement of the pulmonary outflow tract, with or without concomitant pulmonary insufficiency, did not interfere with normal cardiac function. Bakos[2] destroyed almost the entire free right ventricular myocardium by electrocoagulation in acute experiments in dogs and found that the pulmonary arterial pressure remained constant. Starr, Jeffers, and Meade[8] in similar experiments could demonstrate no conspicious increments in systemic venous pressure. Following complete occlusion of the right coronary artery at its aortic origin, Donald and Essex[4] could demonstrate little change in the atrial, caval, pulmonary arterial or carotid pressures. Our observations concerning systemic arterial and venous pressures in the acute stage following resection of large segments of right ventricular myocardium and replacement with fabric grafts are similar. In addition, the present work indicates that animals can survive such operations for prolonged periods without detrimental effects on the circulation.

The ability of the heart to compensate for various insults to right ventricular myocardium is striking. Normal pressure relationships in the right side of the heart and normal cardiac output are maintained despite absence of normally contracting right ventricular musculature. Two important factors in the maintenance of ventricular function are preservation of a reasonably normal diastolic volume and the absence of paradoxical motion in the ventricular myocardium. It is apparent that any significant dissimilarity in the diastolic filling volume of the two ventricles will lead to cardiac decompensation. Paradoxical motion of large segments of ventricular myocardium diminishes cardiac

output by alteration of the systolic ejection volume as seen clinically in patients with ventricular aneurysms. The feasibility of replacement of large portions of right ventricular myocardium with fabric is dependent upon maintenance of a normal ventricular volume and the use of a nonexpansile replacement.

Various explanations have been advanced for the preservation of right ventricular function following extensive anatomic damage. Donald and Essex[4] postulated that a small amount of functional right ventricular muscle was sufficient to maintain an adequate pulmonary flow, if an additional load (i.e., mitral stenosis) were not superimposed. The most logical explanation to us is that postulated by Bakos.[2] Four main, distinct, and independently contracting ventricular muscle bands comprise musculature common to both ventricles in dogs and human beings. These include the superficial and deep sinospiral and bulbospiral muscles. Each of the superficial muscles partially encircles both ventricles but, considered together, they completely envelop, in a supplementary manner, the whole surface of the heart. The deep sinospiral muscle completely encircles both ventricles but splits so that the greater mass of fibers projects deeply and enters into formation of the interventricular septum. The deep bulbospiral muscle is confined to the left ventricle. Because of this encircling arrangement, Bakos suggested that the tension developed during contraction of the undamaged portion is mechanically transmitted through this anatomic continuity to the damaged or nonfunctioning right ventricular portion. It is thus possible for the right ventricle to maintain a normal output and pressures despite extensive damage.

While this study was not primarily intended as an evaluation of the fate of synthetic materials implanted in the myocardium, certain observations are pertinent. In our limited experience, woven Teflon fabric was the most satisfactory material for replacement of right ventricular myocardium. Blood loss through the fabric was negligible and suturing was easy. Although Teflon felt can be sutured easily, moderate blood loss occurs even after preclotting. In general the Teflon provoked little inflammatory reaction and no intraventricular thrombi. No contracture was observed with the Teflon replacements but observation periods were too short to warrant any definite conclusions regarding this possibility.

Dobell and associates[3] previously evaluated Ivalon as a replacement for right ventricular myocardium and considered it to be unsatisfactory because the patches developed fibro-cartilage and calcification. These findings are at variance with those of Sauvage and associates[7] who regarded Ivalon as a highly satisfactory material in this location. Although the Teflon patches used in this study were well covered with fibrous tissue, the reduced porosity apparently precluded permeation by fibrous tissue. The necessity or desirability of fibrous tissue infiltration of grafts in this location is not settled.

The data from this experimental study indicate that resection of large portions of right ventricular myocardium is feasible if the resected portion is replaced with a fabric graft. The results are sufficiently encouraging with the right ventricle that we have started similar studies with left ventricular resection and replacement.

SUMMARY

In a series of dogs, large portions of the right ventricular myocardium were excised during cardiopulmonary bypass. The resected portion was replaced with Teflon fabric of appropriate size. In one group of animals, myocardial infarction was produced prior to resection. The mortality rate was high, due chiefly to pulmonary complications and inadequate resection of infarcted muscle. In the survivors, cardiac output and pressure in the right side of the heart remained normal. The most significant factor in preservation of right ventricular function following resection and graft replacement is the encircling arrangement of muscle bundles, permitting mechanical transmission of tension from the undamaged to the damaged myocardium. The woven Teflon fabric used as a patch healed well without infection or thrombosis. This study indicates that large portions of right ventricular myocardium may be resected and replaced with prosthetic material without adverse effects.

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(For Discussion, see page 779)

BLOOD-BRAIN BARRIER STUDIES IN EXTRACORPOREAL COOLING AND WARMING

Harry S. Pollard, Jr., Lieutenant, MC, USN (by invitation), Robert J. Fleischaker, Captain, MC, USN** (by invitation), Joseph J. Timmes, Captain, MC, USN,*** and Karl E. Karlson, M.D.,*****
St. Albans, N. Y.

THE rapidity with which profound hypothermia is produced by blood stream cooling with extracorporeal circulation and the advantages it offers in aiding the correction of certain cardiovascular lesions under direct vision have led to the widespread use of this modality.[1, 2]

At 30° C., the solubility of oxygen in water is 2.6 vol. per cent, whereas at 0° C., the solubility has increased to 4.89 vol. per cent. Thus, it is easily seen that two potential hazards of gas embolism exist in the clinical application of extracorporeal warming and cooling. If blood equilibrated with oxygen at low temperatures is infused into the normothermic patient, it is possible that oxygen in physical solution at the low temperature may be released on warming in the form of small gas emboli. If blood equilibrated with oxygen at low temperature is warmed in a heat exchanger, bubbles may form in the extracorporeal circuit and subsequently be infused into the patient.

From a theoretical standpoint, it would seem advantageous to accomplish extracorporeal cooling with the heat exchanger in the arterial limb of the circuit, so that blood is cooled after equilibration with oxygen, and to perform warming on the venous limb of the extracorporeal circuit, prior to equilibration with oxygen. The achievement of hypothermia by a period of partial perfusion (withdrawal of blood from the superior vena cava, oxygenation, and infusion into the femoral artery) as practiced by Sealy and Brown and their associates,[3] seems to offer a theoretical safety mechanism in the avoidance of intravascular gas embolism during extracorporeal cooling.

From the U. S. Naval Hospital, St. Albans, Long Island, N. Y.

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The opinions expressed herein are entirely those of the writers and are not necessarily those of the Department of the Navy or Department of Defense.

*Surgical Research Laboratory, U. S. Naval Hospital.

**Department of Thoracic Surgery, U. S. Naval Hospital.

***Chief of Surgery and Assistant Professor of Surgery, State University of New York, Downstate Medical Center, Brooklyn, N. Y.

****Professor of Surgery, State University of New York, Downstate Medical Center, Brooklyn, N. Y.

With this technique, the refrigerated blood is infused into the lower one half of the body only; the cardiac output to the upper one half being supplied by the patient's heart. In addition to allowing more even cooling, the technique requires any bubbles formed in the lower body to pass through the capillary bed of the lower part of the body and the lungs prior to circulation to the central nervous system, until the temperature differential between the patient's body and the infused blood has been reduced. If the site of infusion were into the upper half of the body, the intravascular occurrence of gas emboli in the central nervous system would seem possible.

The above considerations of potential gas embolism in the course of extracorporeal cooling and warming led to this study of the optimum method of clinical conduction of extracorporeal cooling with respect to: (1) the temperature differentials involved in and required for the production of gas embolism during blood cooling and warming, (2) the optimum site of placement (venous

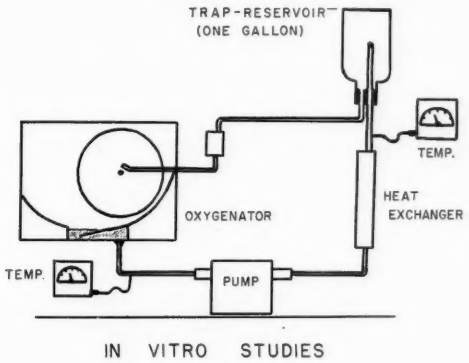

Fig. 1.

and arterial) of the heat exchanger in the application of extracorporeal cooling and warming, (3) the site (distal or proximal aorta) of infusion of refrigerated blood into the normothermic animal offering minimal risk of gas embolism to the central nervous system, and (4) the advantage, if any, of the period of partial perfusion to lower the temperature gradient between patient and infused blood during cooling.

Hodges and co-workers[4] showed that the blood-brain barrier to intravenously administered sodium fluorescein is damaged by embolism. Under the conditions of the present experiment, the disruption of the blood-brain barrier is presumptive evidence of gas embolism.

METHODS

I. *In Vitro Perfusions.*—

A modified Dennis oxygenator was used with a parallel tube-type heat exchanger to perfuse a one gallon capacity bubble trap (Fig. 1). Bubble formation was studied during the warming and cooling of outdated, ACD, banked blood with the heat exchanger in various locations in the extracorporeal circuit. Temperatures were monitored at multiple sites in the circuit with a calibrated YSIC telethermometer.

II. *In Vivo Perfusions.*—

Seven groups of animals were studied using the modified Dennis oxygenator and Sigmamotor pump (Fig. 2). A parallel tube heat exchanger was used for achievement of hypothermia and restoration of normothermia. The normothermic perfusions were performed at a flow rate of 100 c.c. per kilogram per minute. In hypothermic perfusions, the flow rate

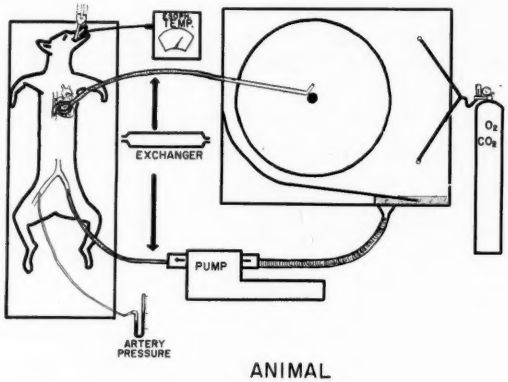

Fig. 2.

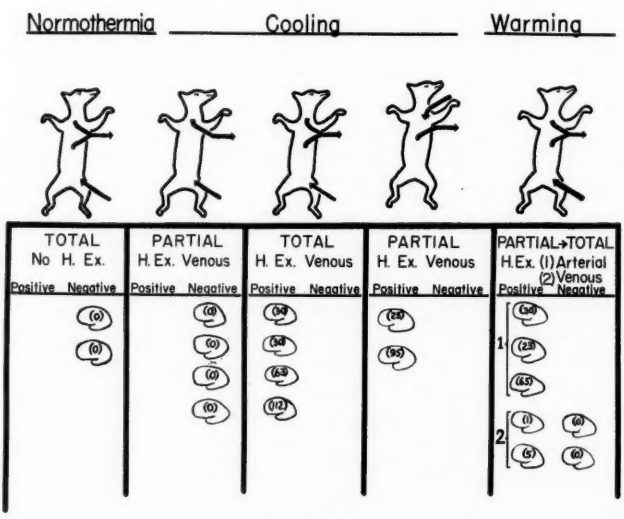

Fig. 3.

was reduced approximately 3 per cent per degree centigrade reduction of esophageal temperature. In animals cooled by partial perfusion, cardiac action was noted to become ineffectual when a temperature of 25° to 20° C. was reached, at which time the animal was placed on total perfusion. In all instances, a mean arterial pressure of at least 70 mm. Hg was maintained during perfusion. The heat exchanger was in the venous line for all perfusions except those of Group 5. The method of cannulation is summarized in Fig. 3 for each group.

Thirty minutes prior to the termination of each perfusion, 25 mg. per kilogram of sodium fluorescein was administered intravenously. After the 30 minute period of perfusion with fluorescein, the animal was sacrificed and the brain was removed. Seven coronal sections of the brain were made and examined under the ultraviolet light. The areas of fluorescence were counted and the brains graded according to the method of Hodges and Associates.[4] (Table I.) Any brain showing areas of 3 mm. or more in size was automatically considered as 4+.

TABLE I

AREAS FLUORESCENCE (NO.)	GRADE
0	Negative
1-3	Trace
4-5	1+
6-10	2+
11-15	3+
16- or more	4+

Controls.—

Normothermic perfusion for one hour.

Hypothermia Controls.—

Under pentobarbital anesthesia, 250 to 300 c.c. of arterial blood (equilibrated with room air in vivo) was drawn in a plastic bag containing heparin and cooled in such a manner that further solution of gas was not possible. During the cooling of the blood, an internal carotid artery was exposed and, after heparinization of the animal, cannulated with a polyethylene tube. When the blood reached a temperature of 10° C. in the bag, it was infused into the carotid artery under pressure over a 2 minute period (flow approximately 125 to 150 c.c. per minute) (Fig. 4). Fluorescein was given intravenously and the animals were sacrificed for study of the blood-brain barrier (BBB).

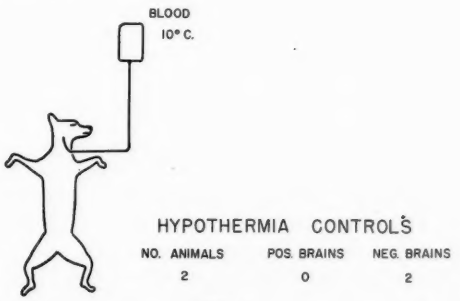

Fig. 4.

Rapid Extracorporeal Cooling.—

GROUP I. *Partial perfusion via femoral artery:* Cooling was accomplished by withdrawal of blood from the superior vena cava, refrigeration, oxygenation, and infusion via a femoral artery. Blood in the arterial reservoir at the beginning of the experiment was at a temperature of 8° to 12° C. Fluorescein was administered when a temperature of 12° C. (esophageal) was reached. After 30 minutes, the BBB was studied.

GROUP 2. *Partial perfusion via aortic arch:* Cooling was accomplished as above except that caval drainage was via the inferior vena cava, and infusion was into the aortic arch through a cannula inserted in a brachiocephalic artery.

GROUP 3. *Rapid cooling with total perfusion:* Both the superior vena cava and the inferior vena cava were cannulated for venous drainage; blood was infused via a femoral

artery after refrigeration and oxygenation. After cannulation, the animal was placed on total cardiopulmonary bypass without a period of partial perfusion. The blood in the arterial reservoir at the beginning of perfusion was 8° to 12° C. When an esophageal temperature of 12° C. was achieved, fluorescein was given intravenously and after the perfusion period of 30 minutes, the BBB was studied as previously described.

Rapid Extracorporeal Cooling and Warming.—

GROUP 4. *Partial perfusion cooling—warming with heat exchanger in venous line:* Extracorporeal cooling conducted in identical manner to Group 1 until the temperature was approximately 12° C. Warming was accomplished by circulating water at a temperature of 42° C. in the jacket of the heat exchanger until the esophageal temperature rose to 33° to 34° C. Fluorescein was given and the animals were sacrificed after an additional 30 minute perfusion for study of the BBB.

GROUP 5. *Partial perfusion cooling—warming with heat exchanger in arterial line:* Cooling was conducted as in Group 4. Warming was accomplished with the heat exchanger in the arterial line. Circulating water bath was 42° C. as above.

RESULTS

In Vitro Perfusions.—

Cooling: Thirty cooling studies of banked blood failed to reveal the formation of bubbles in the in vitro circuit, regardless of the temperature change as measured pre- and post-passage of the blood through the heat exchanger.

Warming: Twenty in vitro perfusions revealed that warming of blood previously cooled to 12° C. consistently produced a steady release of bubbles if the temperature gradient pre- and post-passage through the heat exchanger was maintained at 10° C. for more than 5 minutes.

Control Perfusions.—

Normothermic control perfusions: Two animals that received a normothermic perfusion for one hour had no fluorescent areas in the brain.

Hypothermia controls: The 2 animals which received perfusion of the carotid artery with blood at 8° to 12° C. previously equilibrated with gas at room temperature had no fluorescent areas in the brain.

Rapid Extracorporeal Cooling.—

GROUP 1. *Partial perfusion cooling via femoral artery:* Two animals were perfused using this technique. Both had brains that were negative.

GROUP 2. *Partial perfusion cooling via aortic arch:* Both animals in this group has 4+ brain (25 and 95 areas with gross confluence of fluorescence).

GROUP 3. *Rapid cooling with total perfusion:* All 4 animals in this group had 4+ brains (30 to 112 fluorescent areas with gross confluence).

GROUP 4. *Partial perfusion cooling—warming with heat exchanger in venous line:* Four animals comprised this group; 2 presented negative brains, one had a trace (1 area), and one was 1+ (five areas).

GROUP 5. *Partial perfusion cooling—warming with heat exchanger in arterial line:* All 4 animals revealed 4+ brains (30 to 65 areas of fluorescence) with some confluent areas of fluorescence.

DISCUSSION

Our in vitro observations roughly parallel those of Donald and Fellows[5] who reported the production of bubbles when a temperature rise (Δt) of 17° was produced by passage of blood through a heat exchanger. They further determined that an increase of pO_2 of 70 mm. Hg or more occurred during warming, when bubbles were formed. Those authors noted a time lag of 10 minutes prior to the appearance of bubbles in their bubble trap. Under the conditions of the present study, a lower Δt (10° C.) was found to result in visible bubble formation and the time lag in this study was considerably shorter (2 to 5 min). When the Δt, resulting from passage of blood through the heat exchanger, was kept below 10° C. we were unable to identify the formation of visible bubbles.

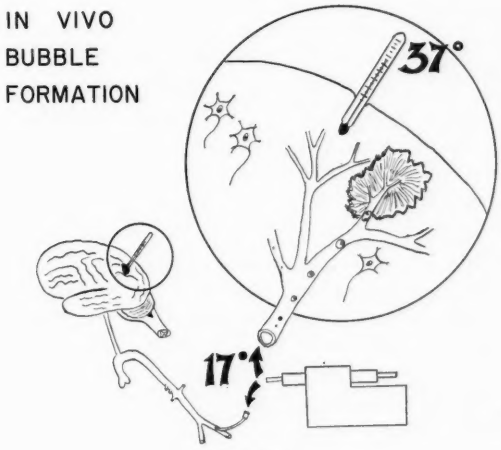

Fig. 5.

Routine measurements in the course of our clinical perfusions in which hypothermia is employed have revealed that the temperature of the blood in the arterial reservoir immediately after priming is approximately 10° C. After recirculation and oxygenation, the temperature rises to 15° to 17.5° C. The in vitro measurements during cooling have disclosed blood leaving the heat exchanger at a temperature of 17° or lower, even early in the course of cooling.

When the blood at the above temperatures is infused into a normothermic animal, the conditions shown to produce bubbles in vitro are not only met but are exceeded (Fig. 5). Thus, the physical requirements for intravascular formation of gas emboli are readily accomplished during the course of extracorporeal cooling. If the patient is immediately placed on total perfusion[6] or if the cold blood is infused into the area of the cerebral vessels, the gas embolism can involve the central nervous system.

If the temperature of the body is lowered during partial perfusion via the femoral artery as described by Sealy and Brown and co-workers,[3] it is possible

to avoid the formation of gas emboli in the central nervous system vessels, presumably on the grounds that: (1) gas emboli forming in the lower one half of the body are filtered out in the capillaries of the abdominal organs, lower extremities, and the lungs, and (2) the temperature differential between the infused blood and the patient's tissues in the upper half of the body is lowered evenly so that a Δt sufficient to cause release of bubbles is not encountered. Any bubbles introduced after formation in the extracorpeal circuit would have a chance of being removed via the natural "bubble trap" of the renal arteries, superior mesenteric artery, and celiac artery prior to gaining access to the central nervous system circulation, and may explain the slightly lower numbers of fluorescent areas seen during warming with the heat exchanger in the arterial line.

SUMMARY AND CONCLUSIONS

This experiment demonstrates that bubbles may be released from blood which has been equilibrated with oxygen at profoundly hypothermic temperatures if the temperature is raised 10° C. by passage through a heat exchanger in vitro. Since these conditions are encountered in the clinical management of extracorporeal cooling and warming, it is possible that injury to the central nervous system may occur, either from intravascular bubble formation or from infusion of gas emboli formed in the extracorporeal circuit.

The embolization secondary to release of gas from physical solution in extracorporeal circulation can be avoided by: (1) a period of partial perfusion during cooling, whereby the temperature differential between blood and body tissues, is gradually lowered, (2) infusion of blood into the lower half of the body rather than the aortic arch, and (3) warming of blood proximal to an adequate bubble trap in order that bubbles formed upon heating of blood are not infused into the patient. In these experiments, the oxygenator has been shown to be an efficient bubble trap at flows up to 3,500 c.c. per minute.

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Discussion

(Papers by Remillard [Page 709], Dammann [Page 722], Drake [Page 735], Dagher [Page 743], Madoff [Page 755], Collins [Page 764], Pollard [Page 772], and Their Associates)

DR. GEORGE H. A. CLOWES, JR., Cleveland, Ohio.—I would like to address my remarks to the paper by Dr. Frank Dammann and that of Dr. Ibrahim Dagher. Some years ago—in 1953—my associates and I got together the people who had had operations on the mitral valve and demonstrated that the arterial hypertrophy, as measured by lumen:wall ratio, was proportional to a product of the time that the patient had had symptoms and the pressure. We wondered how to obtain a subsequent biopsy of the lung to examine again and find out what happened to the pulmonary vessels after correction of the pulmonary hypertension. Recently a patient returned to me with a tumor in the lower lobe, which we took out, and much to our interest we found that this woman's lumen:wall ratio had returned to the normal value, after having been extremely low 7 years before.

I think everybody who performs operations for mitral stenosis sees patients who take 6 months to a year to attain their maximum improvement from the operation. Doubtless this is in some part related to the change in the vascular component.

Now about Dr. Dagher's paper, this is a wonderful thing to have a man from the American University of Beirut with us here presenting such a fine piece of work. He has added further to our knowledge in an important field. We have been interested for years in what hypoxia does to people and to animals, and his work confirms and supplements the experiments of J. deBerg Daly, and more recently those of Peter Salisbury, on the effects of hypoxia on the vasculature of the lung. These show that the presence of hypoxia in the arterial blood entering the chemorecytoid of the carotid sinus causes a reflex constriction of the pulmonary arterioles. The effect is abolished by thoracic sympathetic nerve section.

It would appear, from his experience, that this might explain to some extent the difficulties we see after operation. For example, the person who is operated upon for pulmonary stenosis and develops right ventricular failure with a low cardiac output may have an increase in the pulmonary vascular resistance. Should pneumonia be superimposed subsequently, and hypoxia result, the situation would be aggravated. The pulmonary resistance might be increased, and death from right-sided failure would be the outcome. Obviously, failure of the ventricle is the main thing but the sympathetic arteriolar component probably plays an important part, especially in those people who have already a pulmonary hypertension. I think we have all seen cases that would suggest that he is right.

I would like to draw attention to one other thing. We all know that a sympathectomized, adrenalectomized animal dies very rapidly from severe hypoxia, far more rapidly than the animal which is intact—3 minutes as compared to 10 minutes—when made to breathe 100 per cent nitrogen. I would say that this probably plays a part in Dr. Dagher's story. In other words, the left ventricle is affected by the removal of the sympathetic nerves and probably does not function as well as that supplied with norepinephrine from the accelerator nerves. In other words, this would account in part for the increase in venous pressure that takes place under the circumstances.

DR. OSLER ABBOTT, Atlanta, Ga.—I rise primarily to expand a bit three things which Dr. Dammann discussed with us: first, a slight modification of the emergency narrowing of the pulmonary artery which one should do if, on opening the chest, the cardiac action is weak. In such emergencies we have employed a short empty sponge forceps to grasp the left lateral wall of the main pulmonary artery and so apply it as to narrow the diameter of that artery about 30 to 40 per cent. This clamp may be left in place during the dissection around the base of the pulmonary artery. Sufficient improvement with this has occurred that we have subsequently used it as a routine initial maneuver in these patients as soon as we enter the pericardium.

There is also the problem of patients of this type who present evidence of left lower lobe or total left lung atelectasis. In reviewing our own patients, we found that every

infant who has presented significant atelectasis of the left lung, and who was not operated upon, died within 3 to 4 months. The gravity of this finding, I think, needs stress. In fact, Dr. Dammann once suggested that the presence of total atelectasis of the left lung was, in itself, indication for emergency surgery.

Third, one may encounter a profound diuresis in the first 24 hours after adequate pulmonary artery banding. An indwelling urinary catheter with hourly monitoring of output should be a standard postoperative maneuver in these patients.

DR. JOHN E. CONNOLLY, San Francisco, Calif.—At Stanford we have been using radioactive techniques to measure coronary blood flow for the past 2 years. [Slide] We originally used it to evaluate the efficacy of bypass procedures. This is the washout curve of Na^{22}. Here is where the sodium is injected into the left ventricle. This is the normal washout curve. Here is the curve where sodium is injected when the heart is under a load due to pulmonary artery constriction and, then, when the bypass is started, you see the increase in the coronary blood flow, as represented by a steeper washout curve.

Below this is the logarithmic plot of the turnover rate expressed in per cent per minute.

These isotope measurements that we made of coronary blood flow correlated very well with direct coronary artery measurement which was performed by a cannula in the coronary sinus. The advantage of this isotope technique is, of course, that it can be used with a closed chest employing, as Dr. Madoff did, a left ventricular puncture technique.

However, it is only a relative guide or relative measure of coronary blood flow, and to be meaningful it has to be compared with a pre-existing measure of coronary blood flow.

DR. BENSON B. ROE, San Francisco, Calif.—Dr. Collins and his colleagues have very convincingly shown us the dispensability of parts of the right ventricle, but I think it would be wrong if any member of this group obtained therefrom a feeling of complacency in the use of the tightly woven Teflon as the most ideal tissue replacement. Perhaps the tissue in the dog behaves differently than it does in the human, and there is evidence to suggest this because of the dog's greater propensity toward intraluminal clotting.

The specimens he showed us do, indeed, convincingly demonstrate a pseudoendothelium and a pseudoepicardial coverage to his graft, but I would like to draw your attention to the very excellent work recently reported by Wisloski and his colleagues indicating that this tightly woven material, particularly Teflon with its nonwettability characteristics, behaves very poorly. Arterial woven Teflon grafts have had an extremely high incidence of pseudoaneurysms and have had to be replaced.

When these are re-examined at operation or autopsy, it is interesting to note that there is no healing at the junction between the woven Teflon and the aorta or in the endocardium. The sutures are all that is holding the graft.

Although I am sure that most of you have used this material and have got away with it under most circumstances, you will probably have difficulty with it sooner or later. I had the misfortune of re-operating on a patient with an atrial defect closed with a woven Teflon patch which showed no evidence of healing after 8 weeks.

Another patient with a tetralogy of Fallot, in whom this material was used in the outflow tract, had a huge aneurysm a year later and the Teflon patch embolized into the pulmonary artery.

DR. DAMMANN (Closing).—I think what Dr. Clowes emphasized deserves to be re-emphasized. It takes time for pulmonary vascular changes to regress. Although we would like to see that changes have occurred in the pulmonary vessels of our older patients in whom the pulmonary artery was stenosed, we believe that we must wait 5 to 6 years to permit maximum change.

In regard to Dr. Abbott's remarks, we have lost 6 patients before the pulmonary artery could be isolated. This just serves to emphasize how acutely ill the small baby with a ventricular defect may be. Among the infants in our series, there have been a number with left lower lobe atelectasis and, frequently, with right upper lobe atelectasis. Undoubtedly, this complication adds to the risk of operation. However, it makes surgery even more mandatory.

DR. MADOFF (Closing).—I would like to point out that the technique described by Dr. Connolly would seem to estimate total coronary blood flow. The method on which we have been working appears to measure coronary blood flow from a local area and may have some advantage if, during operation, one can rapidly change the total coronary blood flow to a single area and thus be able to detect it with a single injection of NaI^{131} at the local site.

DR. COLLINS (Closing).—I think Dr. Roe's word of caution is well taken. We were not attempting primarily to evaluate materials in this location but were somewhat at a loss to know exactly what to use. Dr. Dobell in somewhat similar experiments felt that Ivalon was relatively unsatisfactory. Dr. Gross' group recently evaluated a large number of substances in the right ventricular musculature of the outflow tract and it was my impression from their work that they felt that Teflon was an acceptable material. I don't think this issue is finally settled.

HEMODYNAMIC AND METABOLIC RESPONSES OF THE WHOLE BODY AND INDIVIDUAL ORGANS TO CARDIOPULMONARY BYPASS WITH PROFOUND HYPOTHERMIA

Thomas J. Yeh, M.D. (by invitation), Lois T. Ellison, M.D. (by invitation), and Robert G. Ellison, M.D., Augusta, Ga.

SINCE the feasibility[1] and advantages[2, 3] of combining profound hypothermia with extracorporeal circulation have been demonstrated, this invaluable adjunct for cardiac surgery has found acceptance and wider use among surgeons.[4-7] This study was designed to investigate in dogs some of the alterations in hemodynamics and metabolism of the whole body and some of the individual organs associated with extracorporeal circulation and hypothermia.

METHODS

In Group I, the effects of cardiopulmonary bypass and profound hypothermia upon the whole body were studied in 16 experiments. Adult mongrel dogs, weighing 10 to 20 kilograms, were premedicated with morphine sulfate (2 mg. per kilogram of body weight) and atropine sulfate (0.4 to 0.6 mg.), and lightly anesthetized with intravenous Nembutal (10 to 15 mg. per kilogram). Ventilation was maintained with a pneophore demand valve and 100 per cent oxygen. Mid-esophageal temperature, femoral artery pressure, superior vena cava pressure, and electrocardiogram were monitored continuously with a Grass polygraph recorder. After right thoracotomy was performed, venae cavae were cannulated though the right atrium and the left atrium was cannulated through the base of the right middle lobe vein. The dogs were placed on total cardiopulmonary bypass using an 11 inch Kay-Cross disc oxygenator and a De Bakey roller pump set nearly occlusive. Profound hypothermia of 5° to 10° C. (esophageal) was produced with a Brown-Harrison heat exchanger inserted into the arterial inflow line to the femoral artery. Arterial and mixed venous samples were obtained (1) before bypass, (2) shortly after going on bypass at normal temperature, (3) at 25° C. while cooling, (4) below 10° C., (5) at 25° C. during rewarming, and (6) again at normal temperature after coming off bypass. Arterial and venous oxygen saturation, arterial pH, Pco_2, bicarbonate, hematocrit, and blood sugar were determined. Oxygen saturation was by cuvette oximetry, pH by Cambridge research model pH meter corrected to the temperature of blood sampled, P_{CO_2} by Riley bubble equilibration method, and bicarbonate by subtraction of dissolved CO_2 from total CO_2 obtained from Van Slyke analysis. Flow rates, calculated by revolutions per minute of pump head and stroke volume, were varied between high (above 50 c.c. per kilogram per minute) and low (below 50 c.c. per kilogram per minute).[8] Reservoir level was used as a monitor of venous return. Oxygen consumption was calculated using the Fick principle. Attempts were made for chronic survival of all dogs.

From the Division of Thoracic Surgery and Department of Physiology, Medical College of Georgia, Augusta, Ga.

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In Group II, the effects of cardiopulmonary bypass upon individual organs were studied in 4 experiments at normal temperature and in 6 experiments when profound hypothermia was used. Anesthesia, thoracotomy, and perfusion were similar to Group I. Arterial inflow was into the left femoral artery and systemic arterial pressure was monitored in the splenic artery. Portal vein pressure was also monitored. Temperatures of mid-esophagus, brain, heart, liver, and thigh muscle were obtained by appropriately placed thermistors. In addition, polyethylene catheters were placed in the jugular, portal, and right femoral veins in such a manner as to avoid obstruction of blood flow. Coronary sinus samples were obtained by direct needle aspiration when it could be done without displacing the heart. Control samples were obtained prior to cannulation of venae cavae to avoid effects of obstruction and decreased cardiac output. Subsequent samples were collected as in Group I. Arterial, mixed venous, jugular, femoral, and coronary venous samples were analyzed for oxygen saturation, pH, and, in some cases, for P_{CO_2} and bicarbonate. Because of the necessary extent of surgery, no attempts were made for chronic survival.

RESULTS

At normal temperature, equilibrium of venous return and arterial inflow was reached shortly after going on bypass. As hypothermia was induced a progressive decrease in reservoir level was noted, indicating accumulation of blood in the dog. When higher flow rates were maintained, the reservoir blood deficit increased to 2,000-2,100 c.c., a quantity larger than the blood volume of the dog. Although similar changes were noted to a less extent in some of the low flow experiments, as a rule there was no appreciable blood loss from the reservoir. Blood lost from the reservoir was partly recovered during rewarming. None of the 4 dogs, in which flow rates were maintained high and in which reservoir deficit exceeded 100 c.c. per kilogram of body weight, survived more than several hours after completion of the experiment. Autopsies showed severe congestion of the liver and portal bed and bloody ascites without evidence of pulmonary edema. In 2 dogs, not included in this series, portal pressure was markedly elevated while inferior vena cava pressure remained normal. There were 5 survivors among 12 dogs when flow rates were reduced to avoid deficit in reservoir.

Hematocrits were constant throughout the perfusion, being unaffected by temperature or blood loss from reservoir. Blood sugar was within normal limits prior to perfusion and showed no appreciable change following perfusion.

Arterial oxygen saturation was 99 to 102 per cent in all dogs throughout the experiments. Venous saturation increased and arteriovenous (A-V) oxygen difference narrowed as cooling progressed. A-V difference was abolished at about 10° C. at higher flow rates. With the onset of rewarming venous oxygen saturation decreased and A-V difference widened, but these changes seemed to lag behind mid-esophageal temperature changes. Thus A-V difference at 25° C. during rewarming was much smaller than at the same temperature during cooling (Fig. 1). At a given temperature, A-V difference appeared to be inversely related to the flow rate. By reducing flow rates as cooling proceeded, it was possible to maintain venous oxygen saturation at 70 to 80 per cent even at a temperature of 5° C. This was done by adjusting flow according to venous saturation determined at intervals of 5 to 6 minutes throughout perfusion (Fig. 2).

Oxygen consumption was reduced not only by hypothermia but also by reduction of flow rates at a given temperature. The same relationship was noted during rewarming. Again it was demonstrated that, during rewarming, oxygen consumption lagged when compared to esophageal temperature changes (Fig. 3).

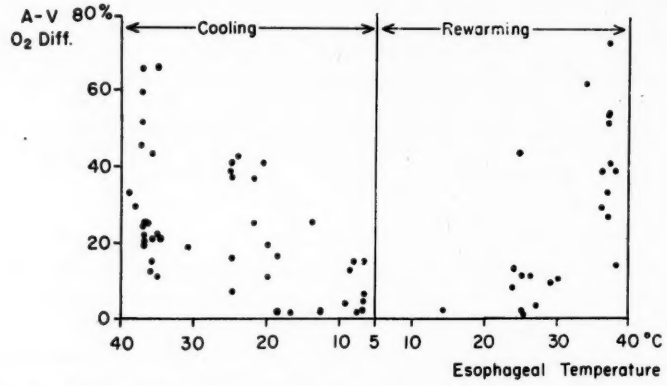

Fig. 1.—Alteration of arteriovenous oxygen saturation difference during cooling and rewarming.

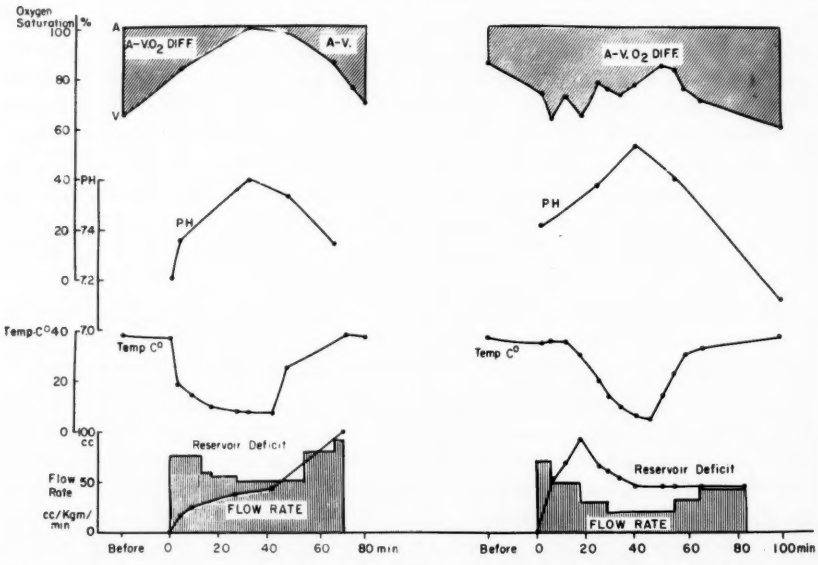

Fig. 2.—Hemodynamic and metabolic alterations during high and low flow hypothermic perfusion.

Varying degrees of mixed acidosis, evidenced by increased P_{CO_2} and decreased serum bicarbonate, were noted prior to going on bypass. As the dogs were cooled, arterial pH invariably increased and, as rewarming proceeded, pH decreased due to the effect of temperature. In the high flow group, with one

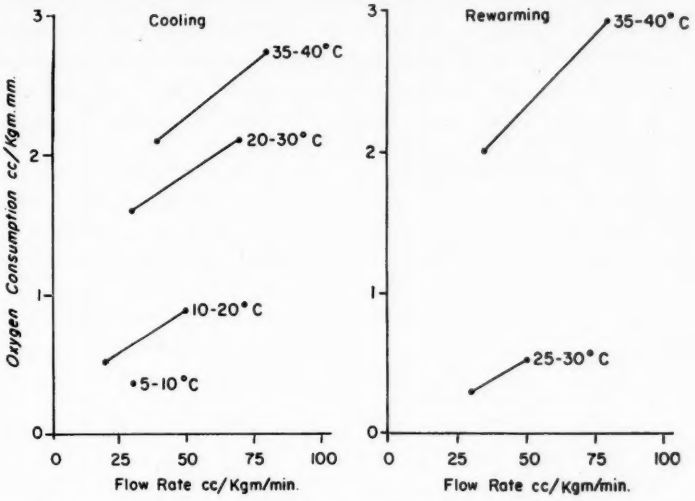

Fig. 3.—Effect of flow rate and temperature on oxygen consumption of whole body during cooling and rewarming.

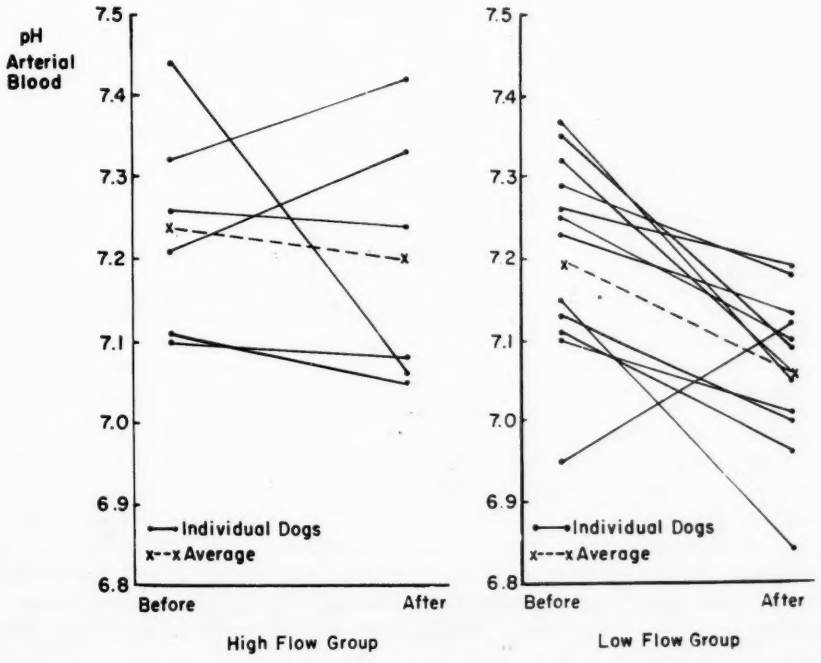

Fig. 4.—pH values of arterial blood before and after bypass with hypothermia using high and low flow rates.

exception, the final pH was not significantly different from the pre-perfusion level. In the low flow group, however, the final pH was significantly lower than the initial level (Fig. 4). In the low flow animals, serum bicarbonate decreased from an average of 21 mEq. per liter before perfusion to 12 mEq. per liter after perfusion. On the other hand Pco_2 values decreased from 53 mm. Hg to 37 mm. Hg. Thus the drop in pH was due entirely to metabolic acidosis.

There were noticeable differences in control values of venous oxygen saturation from various organs (Table I). Femoral vein saturation was constantly lower than other samples except coronary. Portal venous samples tended to be higher, and jugular samples varied in their relation to others. Mixed venous

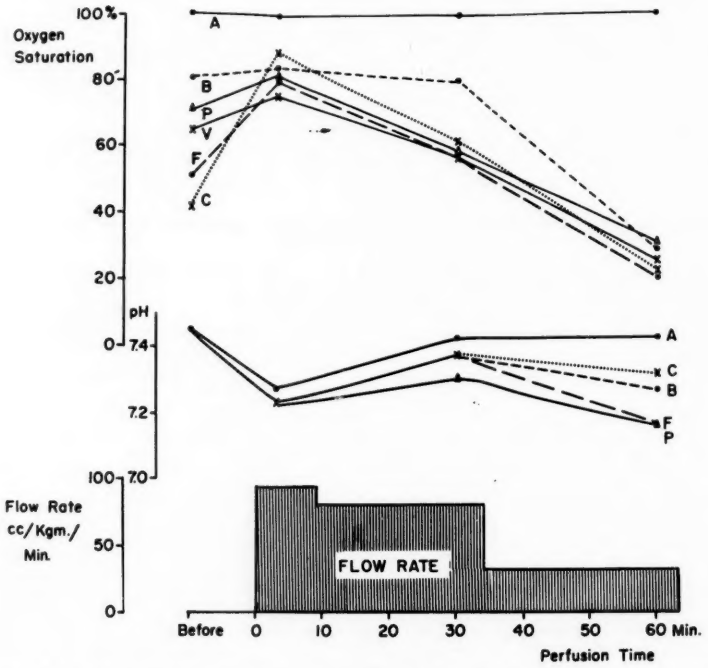

Fig. 5.—Effect of flow rate on oxygen saturation and pH of venous blood from individual organs during normothermic perfusion.

samples averaged 68 per cent whereas arterial saturation was 100 per cent. During normothermic perfusion and with high flow rates of 90 to 100 c.c. per kilogram per minute the various venous samples were within normal range. After low flow of 30 minutes, however, saturation of various venous samples all decreased. This was true whether an interval of low flow preceded or followed an interval of high flow, attesting to the validity of the system and also demonstrating that oxygen saturation changes were not the result of prolonged perfusion.

Reduction of oxygen saturation in venous blood from various organs resulting from low flow at normal temperature was accompanied by decrease in pH

in samples from all organs (Fig. 5). As noted by other investigators,[3, 5] different organs cooled at different rates (Figs. 6 and 7). This was true in both high and low flow groups and the pattern was essentially the same in that the temper-

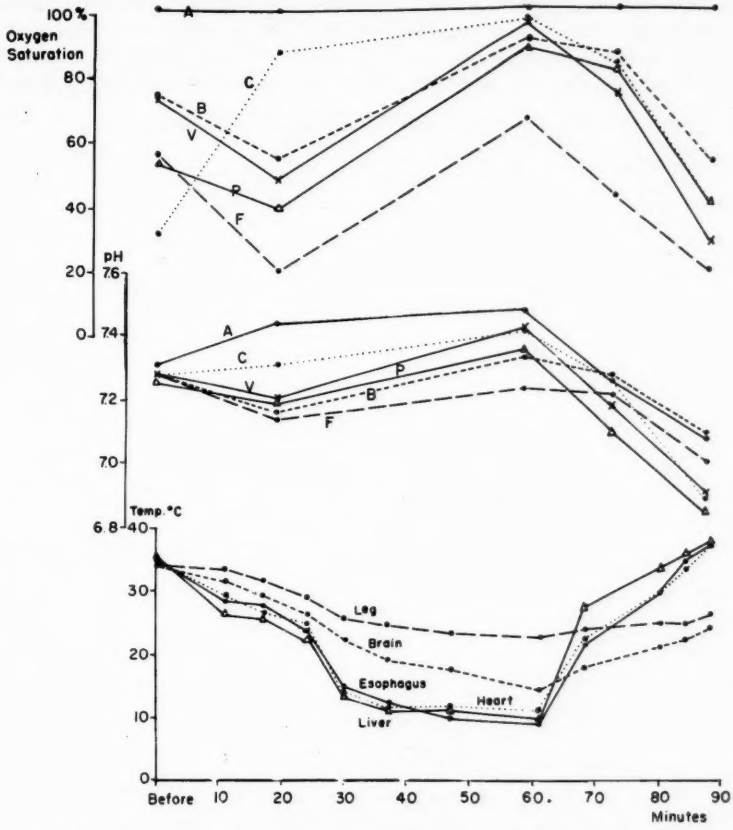

Fig. 6.—Oxygen saturation and pH of venous blood from individual organs and organ temperature (low flow).

TABLE I. CONTROL VALUES OF VENOUS OXYGEN SATURATION FROM VARIOUS ORGANS IN 10 DOGS

DOG NUMBER	PER CENT OXYGEN HEMOGLOBIN SATURATION					
	SYSTEMIC ARTERY	RIGHT ATRIUM	FEMORAL VEIN	JUGULAR VEIN	PORTAL VEIN	CORONARY SINUS
1	99	86	57	61	84	--
2	100	50	40	77	--	--
3	101	58	70	45	70	53
4	101	65	51	81	71	42
5	101	56	18	65	93	--
6	102	80	78	87	81	52
7	103	61	29	78	74	--
8	97	79	49	62	74	64
9	103	75	57	74	54	32
10	100	65	30	65	92	--
Mean	101	68	58	70	77	49

ature of thigh muscle lagged behind that of other organs during cooling and rewarming. The brain also showed a similar trend but to a less extent. Heart and liver temperatures followed closely the general pattern of esophageal temperatures. The temperature gradient between thigh muscle and esophagus was as much as 14° C. to 17° C., and gradient between brain and esophagus was 6° C. to 10° C. and, at times, 13° C. Venous oxygen saturation varied according to the flow rate. Venous oxygen saturation from all organs sampled increased as

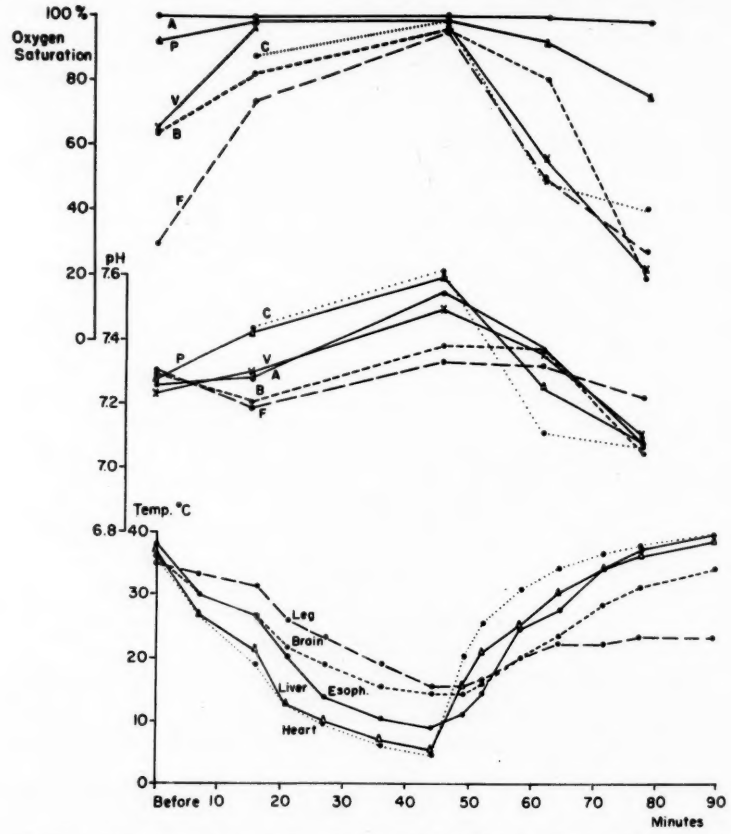

Fig. 7.—Oxygen saturation and pH of venous blood from individual organs and organ temperature (high flow).

cooling proceeded but even at esophageal temperature of 5° to 7° C. A-V differences were not obliterated during low flow perfusion. Femoral venous saturation was consistently lower than that of other samples. After going on bypass, an increase of coronary saturation from the lowest to the highest among the organs was noted. This may be the result of ventricular fibrillation. During high flow perfusion all venous samples approached arterial level, and at 7° C all were above 97 per cent. Again femoral venous samples were lower than the

others but differences were smaller. As rewarming proceeded, venous blood of each organ became less saturated in both high and low flow groups. The pH of mixed venous blood showed fair correlation with the venous oxygen saturation. Blood samples from jugular, femoral, coronary, and portal veins showed similar correlation when the samples from each sampling site were compared, but it was noted that portal vein blood as a whole was better saturated but pH was not higher compared to jugular, femoral, or coronary samples (Fig. 8). The variation probably reflects the characteristics of blood flow and metabolism of each organ.[9-12]

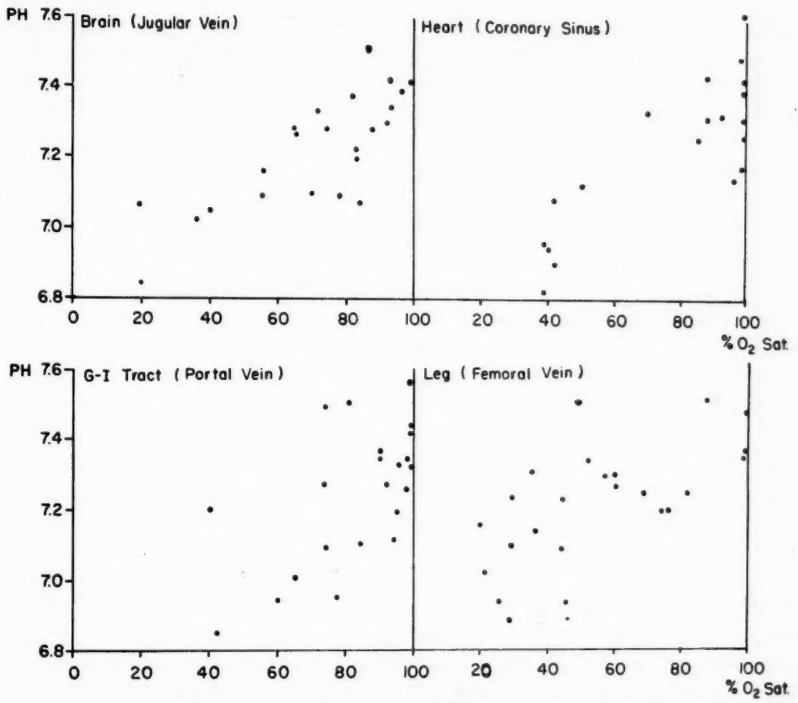

Fig. 8.—pH and oxygen saturation of venous blood from individual organs during cardiopulmonary bypass with hypothermia.

DISCUSSION

The accumulation of blood in the intravascular space during hypothermic perfusion has been reported previously by several investigators.[13-15] Since hematocrits remained constant, fluid accumulated by the dog was interpreted to be whole blood rather than a transudate. This has been attributed to expansion of intravascular space from blockage of the venomotor mechanism by the effect of cold.[15] Accumulation of blood in the portal system, manifested by congestion of liver and abdominal organs and bloody ascites seen in high flow group of dogs, is not an uncommon occurrence in perfusion experiments. Various

factors, such as acidosis, blood reaction, allergy, and endotoxins have been incriminated, but the cause is not completely clear. No new explanation is being advanced to elucidate the etiology or mechanisms, but our studies demonstrated exaggeration of this process by high flow rates during hypothermia. It was also demonstrated that this has a direct bearing on survival.

Oxygen saturation values indicate that even at esophageal temperature of 5° C., tissues continue to consume oxygen as manifested by the A-V difference of 20 to 30 per cent when low flow rates were used. Oxygen consumption was reduced not only by hypothermia but also by reduction in flow rate.[16-18] In other words, even at a temperature of 10° to 20° C., the low flow rate was conducive to lower oxygen consumption. Whereas hypothermia reduces oxygen consumption by virtue of the reduction of metabolic demands of the tissues,[19] the reduction of oxygen consumption, by reduced flow, stems from the relative unavailability of oxygen in abundant supply. pH studies showed that with higher flow rates post-perfusion pH was altered only slightly, whereas with lower flow rates greater shift to acidosis occurred even though venous oxygen saturation was above 70 to 80 per cent, which is a value ordinarily considered adequate for normothermic perfusion. These findings indicate that mixed venous oxygen saturation is not a satisfactory indicator for adequacy of flow during hypothermia. The reason for this is twofold. First, with hypothermia the oxygen dissociation curve shifts to the left.[19, 20] Consequently, the affinity of hemoglobin for oxygen is greater at lower temperatures which, in turn, means less availability of oxygen to the tissues. Lange and co-workers[21] in their study of changes in electrocardiogram in hypothermic rabbits concluded that T-wave changes were due exclusively to tissue anoxia which was attributed to shift of oxygen dissociation curve. By increasing the amount of dissolved oxygen in plasma by use of compression chamber they were able to revert T-wave changes. It is their interpretation that, at tissue tension of 40 mm. Hg, 27 per cent of oxygen in arterial blood is available at 38° C., whereas only 3 per cent is available at 20° C. The figure would be even smaller at 10° C. For this reason, flow rates should exceed those anticipated from reduction in metabolism associated with a given degree of hypothermia. This may appear contradictory to the result of experiments performed by Bigelow and associates[22] in which they concluded that the cooled tissue accumulated no oxygen debt. In their experiments, however, hypothermia was produced by exposure, whereas in this study it was by means of a heat exchanger. The essential difference is that in exposure hypothermia tissues are cooler than blood, but the reverse is the case with core-induced hypothermia. The second reason why mixed venous saturation is not a satisfactory monitor of flow during profound hypothermia is the difference in cooling rates of various organs. Cooling rate presumably varies with blood supply. As esophageal temperature decreases, the heart, liver, and probably other internal organs, such as kidneys and gastrointestinal tract, may cool to about the same degree as the esophagus. This assumption cannot be taken for granted in case of brain which is most susceptible to anoxia. Several investigators noted,[23] as we did, that the brain lagged considerably during cooling and rewarming. Still others[3, 5] noted close correlation between esophageal and brain temperatures. This discrepancy

may be explained by the experiments of Zingg[24] who demonstrated temperature gradients of 7° C. in different parts of the brain of individual animals. Muscle temperatures lagged even more and there is general agreement on this score. Our experiments showed not only slower cooling of thigh muscles, but also lower oxygen saturation of femoral vein blood compared to that of other organs and of mixed vein samples. pH of femoral vein samples remained lower than that from other organs until rewarming was started. At the end of the experiment pH of femoral vein samples was higher. The thigh muscles at this stage (Figs. 6 and 7) were cooler than the remainder of the body, because of the lag of rewarming of the muscle mass. pH of blood is altered by temperature and, if pH of all samples were corrected to esophageal temperature, femoral vein samples would be more acidotic than those from other organs. The lag in cooling and rewarming of certain organs and muscle mass apparently contributes significantly to acidosis in low flow hypothermic perfusion. When the fact that muscle mass constitutes roughly 50 per cent of body weight is taken into consideration, the implication of this becomes even more important. This will also support our view that, in order to avoid acidosis during hypothermic perfusion, flow rate should be set sufficiently high to meet adequately the demands of organs, such as the muscle mass, which are less well supplied with blood and therefore cool more slowly.

SUMMARY

Hemodynamic and metabolic changes were studied in 16 dogs subjected to total body perfusion at various flow rates combined with profound hypothermia of 5° to 10° C. In addition, 10 dogs were perfused in a similar manner and venous blood from various organs was analyzed. Diminution of venous return was noted during cooling. Pooling of blood in intravascular space, particularly in the portal bed, was exaggerated when high flow rates were used. Arteriovenous oxygen saturation difference narrowed with cooling but, even at esophageal temperature of 5° C., tissues continued to consume oxygen. With high flow perfusion, final pH was altered only slightly but, with low flow perfusion, metabolic acidosis developed or was accentuated in spite of seemingly adequate flow, as judged by elevated venous oxygen saturation. In hypothermic perfusion, venous oxygen saturation is not a satisfactory monitor for adequacy of flow. Muscle mass and brain cooled slower than other organs. Femoral venous oxygen saturation was lower than the other samples during perfusion. The possible causes of acidosis which develop after hypothermic perfusion were discussed. In order to avoid serious metabolic acidosis during hypothermic perfusion it appears desirable to adjust flow to the maximum possible without seriously exceeding available venous return.

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(For Discussion, see page 825)

METABOLIC ALTERATIONS ASSOCIATED WITH PROFOUND HYPOTHERMIA AND EXTRACORPOREAL CIRCULATION IN THE DOG AND MAN

William F. Bernhard, M.D. (by invitation), S. Edwin Carroll, M.D.** (by invitation), Hans F. Schwarz, M.D.** (by invitation), and Robert E. Gross, M.D.,*** Boston, Mass.*

In the laboratory and on the Cardiovascular Service of the Children's Hospital, profound hypothermia is induced by incorporating a heat-exchange mechanism in a siphon drainage pump-oxygenator system.[3] Prior to initiating cardiopulmonary bypass, the temperature of the priming blood volume is reduced to 5° to 10° C. during a period of recirculation through the heat exchanger. Commencement of each perfusion with this pre-cooled blood results in a rapid reduction of all recorded temperatures (heart, brain, liver, esophagus, rectum) except that of the muscle mass. Cardiac asystole usually occurs within the first minute of cold perfusion, facilitating immediate cardiotomy. If necessary, the combination of profound hypothermia and extracorporeal circulation permits intervals of total circulatory arrest, or interruption of the coronary arterial circulation alone.

Certain inherent metabolic alterations accompany continuous hypothermic perfusion and are accentuated by periods of circulatory arrest. The least well documented of these involves the development of a metabolic acidosis during the rewarming period characterized by reductions in arterial pH, plasma CO_2 content, and plasma bicarbonate. This increased blood hydrogen ion concentration is dependent upon a number of factors: (1) the rapidity and depth of total body cooling; (2) the presence of a large temperature gradient between muscle mass and the more vascular tissues; (3) development of an oxygen debt which is exaggerated by periods of total circulatory arrest; and (4) temporary cessation of lactate metabolism due to an inhibition of hepatocellular activity below 30° C.

From the Laboratory for Surgical Research, The Children's Hospital Medical Center, Boston, Mass., and the Department of Surgery, Harvard Medical School.

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*Assistant Surgeon, Children's Hospital and Instructor in Surgery, Harvard Medical School.

**Research Fellow in Surgery, Children's Hospital, and Research Fellow in Surgery, Harvard Medical School.

***William E. Ladd Professor of Children's Surgery, The Harvard Medical School, and Chief of Surgical Service, the Children's Hospital.

The current investigation was undertaken to define the pathogenesis and severity of the post-hypothermic acidosis encountered clinically and in the experimental animal.

METHOD AND MATERIALS

A. *Experimental Procedure.*—Thirty mongrel dogs of either sex, weighing 10 to 20 kilograms, were used. Intravenous pentobarbital sodium (30 mg. per kilogram) was administered for anesthesia, and respirations were controlled with a Bennett automatic respirator. Arterial blood pressure was monitored with a Statham P-23D transducer and a Sanborn Twin-Viso recorder. Serial electrocardiograms (Lead II) were also obtained. The temperatures of the heart, brain, liver, and muscle were measured with thermocouples mounted on 22-gauge needles. Additional, thermistor probes were placed in the mid-esophagus and rectum, and the leads were connected to a multiple-channel telethermometer.

A bilateral, anterior thoracotomy was performed in all animals with entrance of the pleura through the fifth intercostal space. After isolation of the venae cavae, sodium heparin (1 mg. per kilogram of body weight) was administered intravenously. Cardiopulmonary bypass was established subsequently, utilizing a Gross model pump-oxygenator system containing a gas mixture of 98 per cent O_2 and 2 per cent CO_2.[9] Prior to bypass, the priming blood volume (2,800 c.c.) was reduced in temperature to the range of 5° to 10° C. by recirculation through the heat exchanger.*[11]

For purposes of obtaining an accurate balance of perfusion blood flow (venous return and arterial output), the disc oxygenator and venous reservoir were mounted directly on a Toledo Scale (Model 4202).† Use of the scale permitted determinations of small changes in extracorporeal blood volume (±2.5 Gm.) throughout the period of extracorporeal circulation.[4]

The cooling phase of each experiment was accomplished in an average of 24 minutes, at which time the brain temperature was reduced to the range of 10° to 15° C. Following an interval of total circulatory arrest (40 minutes in duration), rewarming was begun by circulating warm fluid (42° to 44° C.) through the heat exchanger. The ventricles were electrically defibrillated when the cardiac temperature reached 30° C., and decannulation of the venae cavae was accomplished at a rectal temperature of 32° to 35° C. The mean duration of rewarming was 40 minutes. Upon completion of decannulation, Polybrene (hexadimethrine bromide) was administered intravenously until the clotting time returned to the range of 10 to 15 minutes. Survival data and long-term follow-up studies will be reported separately.[5]

B. *Biochemical Determinations (Animals).*—Arterial blood samples were drawn anaerobically into heparinized, oiled syringes, and the following determinations carried out: (1) whole blood CO_2 content, (2) arterial pH, and (3) plasma lactate concentration. The partial pressure of carbon dioxide expressed in

*Manufactured by International Medical Instrument Company, Stoneham, Mass.
†Toledo Scale Corporation, Brighton, Mass.

millimeters of mercury (P_{CO_2}) was calculated at 37° C. using the Henderson-Hasselbalch equation with a pK′ = 6.10. At reduced body temperatures, P_{CO_2} was computed using values for pK′ (6.10 to 6.30) obtained from the Severinghaus-Stupfel nomogram.[14]

During each experiment, blood specimens were obtained at the following intervals: (1) spontaneous respiration, 37° C.; (2) assisted respiration, 37° C.; (3) end of cooling (10° C.); (4) conclusion of rewarming phase, 34° to 37° C.; (5) assisted respiration during closure of thoracotomy, 34° to 37° C.; and (6) spontaneous respiration (1½ to 3 hours postoperatively), 37° C.

Total oxygen consumption was determined in 19 animals at intervals of 10° C. during cooling and rewarming. The brain temperature served as the standard temperature reference. Simultaneous arteriovenous specimens were obtained and the oxygen determinations (saturation and capacity) were carried out on a Beckman spectrophotometer.[12]

The whole blood carbon dioxide content was determined by the method of Van Slyke and Neill,[15] plasma CO_2 content by the method of Natelson,[11] and plasma lactates according to the enzymatic method of Boehringer.[6]

Arterial pH determinations were performed on a Beckman (Model G) pH meter with a glass electrode assembly immersed in a water bath. The temperature of the bath was adjusted to the "body core temperature"* at the time the blood specimen was obtained.

C. *Clinical Data.*—Open repair of a variety of intracardiac defects was carried out in 35 patients who had esophageal and rectal temperatures in the range of 9° to 23° C. (Table I). In 10 patients (Group I), temperatures were reduced to 9° to 14° C. and, in the remaining 25 patients (Group II), a temperature range of 15° to 23° C. was utilized.

TABLE I. TYPES OF CASES FOR WHICH PROFOUND HYPOTHERMIA WAS EMPLOYED

ANATOMIC DIAGNOSIS	NO. OF CASES (35)
A. Tetralogy of Fallot	15
B. Tetralogy of Fallot with shunt	4
C. Ventricular septal defect with pulmonary hypertension	6
D. Ruptured aneurysm, sinus of Valsalva, ventricular septal defect, and pulmonary stenosis	1
E. Ventricular septal defect and aortic insufficiency	2
F. Valvular and supravalvular aortic stenosis	5
G. Aneurysm circumflex coronary artery communicating with left ventricle	1
H. Total anomalous pulmonary venous drainage	1

Throughout extracorporeal circulation, efforts were made to maintain maximum perfusion blood flows. However, in the cooling phase, reductions of 30 to 60 per cent in total perfusion occurred (from a normothermic standard of 2.4 L. per minute per square meter) due to increments in peripheral vascular resistance and increased blood viscosity. This physiologic flow reduction was always reversed during rewarming.

*The "core" temperature is estimated to be the mean of the esophageal and rectal temperatures.

The mean duration of total bypass in all cases was 91 minutes (range = 28 to 149 min.). Cooling occupied 25 minutes, and rewarming was accomplished in an average of 40 minutes. Interruption of the coronary circulation for intervals of 5 to 55 minutes was necessary in 11 patients to improve visualization within the heart. In 2 other cases, periods of total circulatory arrest were required for a similar purpose.

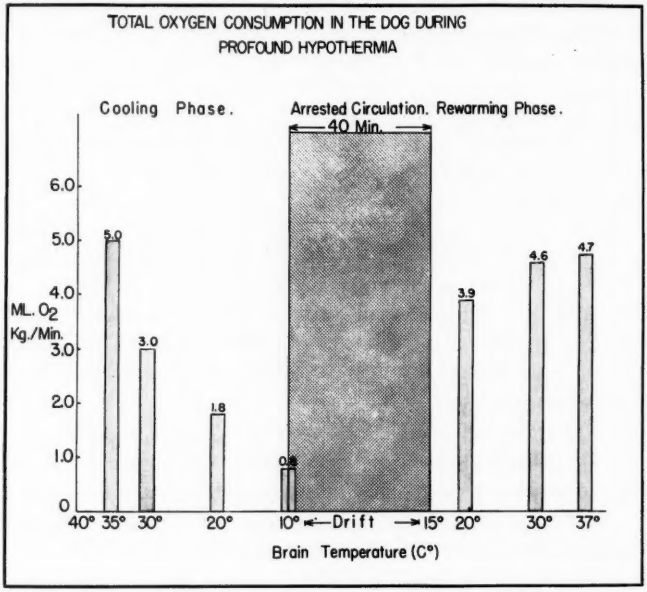

Fig. 1.—This figure contains the mean oxygen consumption data from 19 animal experiments. The increase in consumption during rewarming indicates the presence of an oxygen debt incurred during cooling and the period of circulatory arrest.

D. *Biochemical Data* (Patients).—Arterial blood specimens were obtained for determination of arterial pH, total plasma CO_2 content, plasma bicarbonate, and plasma lactate content. The P_{CO_2} was calculated using the Henderson-Hasselbalch equation as previously described. Samples for analysis were obtained according to the following schedule: (1) assisted respiration at 37° C., (2) 5 minutes after commencement of bypass, (3) lowest temperature during perfusion, (4) end of rewarming, and (5) spontaneous respiration, 1 to 18 hours postoperatively.

OBSERVATIONS

A. *Oxygen Consumption* (Animals).—The changes in oxygen consumption produced by profound hypothermia and a 40-minute period of total circulatory arrest are presented in Fig. 1. These studies disclosed a mean oxygen uptake of 5.0 c.c. per kilogram of body weight per minute at 37° C., 3.0 ± 0.59 c.c. at 30° C., 1.8 ± 0.28 c.c. at 20° C., and 0.8 ± 0.16 c.c. at 10° C. The average perfusion blood flow ranged between 50 and 70 c.c. per kilogram per minute.

During the period of interruption in circulation, a spontaneous 5° upward drift in brain temperature occurred. Therefore, active rewarming was initiated at 15° C., and the oxygen data obtained disclosed: (1) a utilization of 3.4 c.c. per kilogram of body weight per minute at 16° C., (2) 3.9 c.c. at 20° C., 4.6 c.c. at 30° C., and 4.7 c.c. at 37° C. In 5 animals, succinylcholine chloride was administered throughout the rewarming period to eliminate all muscular activity. The mean oxygen upake in these animals was unchanged from the above data.

B. *Biochemical Data* (Animals).—The average whole blood CO_2, P_{CO_2}, plasma lactate, and arterial pH values obtained in the animal experiments are contained in Table II. A decrease in CO_2 content and P_{CO_2} from the control values (37°) was noted prior to cardiopulmonary bypass because of overinflation of the lungs (respiratory alkalosis). This was accompanied by a fourfold rise in plasma lactate content (0.6 mM per liter to 2.7 mM per liter), and an increase in arterial pH (7.39 to 7.57 units). At the conclusion of extracorporeal cooling, the whole blood CO_2 stabilized at 18.6 mEq. per liter and the calculated P_{CO_2} decreased to 12 mm. Hg. These changes were accompanied by a small additional increase in plasma lactate and arterial pH.

TABLE II. MEAN DATA FROM 30 ANIMALS COOLED TO 10° C. AND SUBJECTED TO 40 MIN. OF TOTAL CIRCULATORY ARREST

	SPONTANEOUS RESPIRATION (37° C.)	ASSISTED RESPIRATION (37° C.)	END OF COOLING (10° C.)	END OF REWARMING (36° C.)	ASSISTED RESPIRATION CLOSURE OF THORACOTOMY	SPONTANEOUS RESPIRATION 1.5-3.0 HR. POSTOP. (34°-37° C.)
Whole blood CO_2 content (mM/L.)	19	12	16	15	14	18
P_{CO_2} (mm. Hg)	39	19	12	44	29	38
Plasma lactate (mM/L.)	0.6	2.7	3.1	4.2	—	1.9
pH	7.39	7.57	7.59	7.20	7.37	7.34

At the termination of warm perfusion (following the period of total circulatory arrest), the presence of a metabolic acidosis was documented (mean arterial pH, 7.20; plasma lactate, 4.2 mM per liter). The whole blood CO_2 content remained unchanged (18.8 mEq. per liter), and the P_{CO_2} had returned to normal (44 mm. Hg). Hyperventilation during closure of the thoracotomy transiently reduced the CO_2 content and P_{CO_2}, but later values obtained in the postoperative period revealed: (1) CO_2 content and P_{CO_2} within the normal range, (2) a fall in the mean plasma lactate content toward normal, and (3) an arterial pH of 7.34. Data from a representative animal are contained in Fig. 2.

C. *Biochemical Data* (Clinical Cases).—Table III contains the data obtained from 10 patients (Group I) cooled to the range of (9° to 14° C.). The aberrations in acid-base equilibrium noted here were similar to but less marked

than the changes observed in animals (with total circulatory arrest). These data disclosed: (1) evidence of a respiratory alkalosis (with a twofold increase in plasma lactate) at the beginning of cold perfusion, (2) a further increase in pH and lactate, and a decrease in CO_2 content at the lowest body temperature; (3) a metabolic lacticacidosis (pH 7.28, lactate 2.3 mM per liter) at the conclusion of rewarming, and (4) a return to normal of pH and CO_2 content associated with a drop in plasma lactate, 1 to 5 hours postoperatively (Fig. 3).

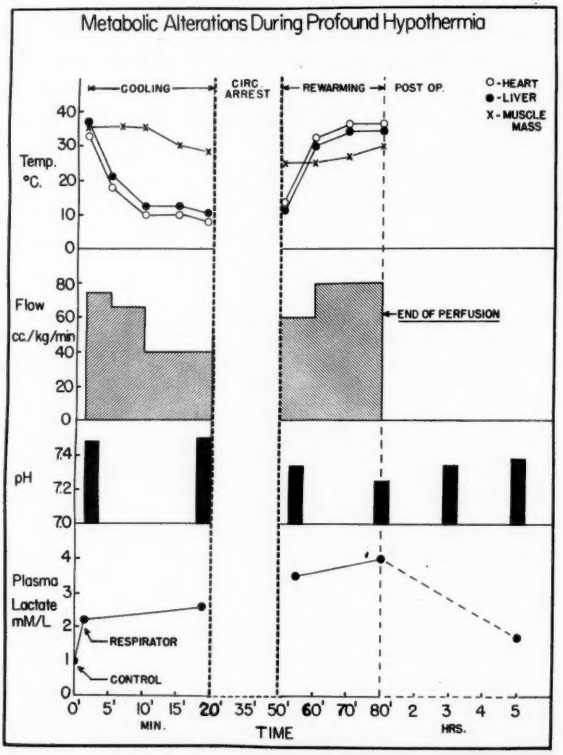

Fig. 2.—This graphic presentation of data from a representative animal experiment illustrates the following: (1) a lag in the cooling rate of the muscle mass when compared to liver and heart, (2) the physiologic reduction in perfusion flow during the cooling phase, and (3) a post-rewarming fall in arterial pH accompanied by an elevated plasma lactate concentration.

An additional 25 patients were cooled to the range of 15° to 23° C. Metabolic data obtained in 10 of them (Group II) are summarized in Table IV. A mild degree of metabolic acidosis was also apparent in these patients at the conclusion of warm perfusion. This was characterized by (1) an elevated plasma lactate (1.8 mM per liter), (2) a decrease in arterial pH to 7.31, (3) no significant change in CO_2 content (18.8 mEq. per liter), and (4) an increase in P_{CO_2} toward the normal range (35 mm. Hg). Spontaneous correction of this acidosis occurred in the postoperative period (Fig. 4).

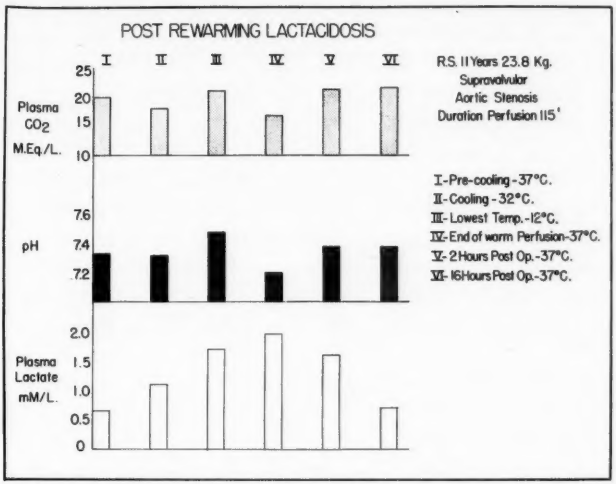

Fig. 3.—This figure presents the acid-base data from a patient of Group I who had surgical correction of a supravalvular aortic stenosis. A post-rewarming lactic-acidosis was evident in Sample IV with spontaneous correction occurring 16 hours postoperatively (Sample VI).

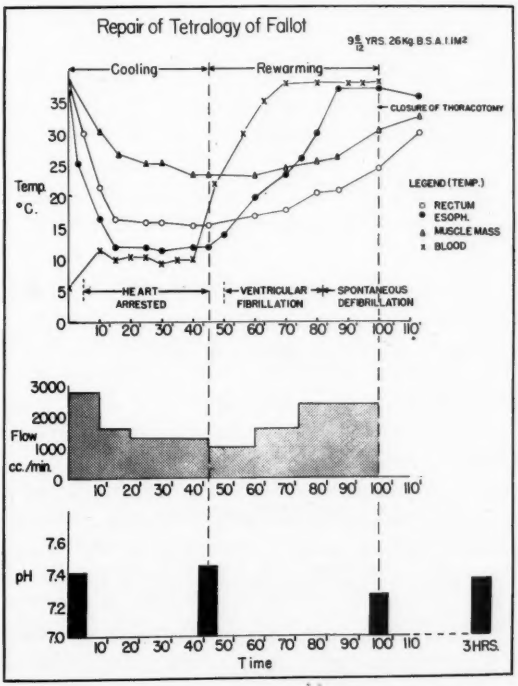

Fig. 4.—This figure records a post-rewarming acidosis (pH, 7.28) in a patient of Group II who had total correction of a tetralogy of Fallot. The arterial pH returned to the normal range (7.40) 3 hours postoperatively.

TABLE III. MEAN DATA FROM 10 PATIENTS WITH RECTAL AND ESOPHAGEAL TEMPERATURE IN THE RANGE OF 9° TO 14° C. (GROUP I)

	CONTROL (37° C.)	BEGINNING OF COLD PERFUSION	LOWEST TEMPERATURE (9°-14° C.)	END OF REWARMING (33°-35° C.)	SPONTANEOUS RESPIRATION 1-5 HR. POSTOP. (37° C.)
CO_2 (mEq./L.)					
Mean	22	20	17	15	20
Range	18-26	18-22	13-22	12-21	17-24
Plasma lactate (mM/L.)					
Mean	0.6	1.4	1.6	2.3	1.1
Range	05-0.9	1.3-1.9	1.5-2.2	1.6-2.4	0.9-1.5
Arterial pH					
Mean	7.39	7.47	7.50	7.28	7.35
Range	7.37-7.42	7.44-7.50	7.40-7.55	7.20-7.41	7.25-7.39

TABLE IV. MEAN DATA FROM 10 PATIENTS WITH RECTAL AND ESOPHAGEAL TEMPERATURES IN THE RANGE OF 15° TO 23° C. (GROUP II)

	ASSISTED RESPIRATION (37° C.)	BEGINNING OF COLD PERFUSION	LOWEST TEMPERATURE (15°-23° C.)	END OF REWARMING (33°-35° C.)	POSTOPERATIVE PERIOD	
					1-5 HR.	6-18 HR.
pH						
Mean	7.37	7.38	7.42	7.31	7.30	7.31
Range	7.23-745	7.28-7.51	7.28-7.50	7.20-7.46	7.22-7.38	7.25-7.37
Total CO_2 (mEq./L.)						
Mean	23.4	20.5	18.6	18.8	19.6	22.9
Range	19.5-30	17-25.1	12.8-23.2	15.6-32.4	16.6-21.2	20.1-24.7
P_{CO_2} (mm./Hg)						
Mean	37	27.6	21.7	35	38.6	41.9
Range	28-47	15-44	14-46	19-69	34-43	41-43
Plasma lactate (mM/L.)						
Mean	0.8	1.5	1.9	1.8	1.8	—
Range	0.4-1.2	1.0-2.1	1.5-2.7	1.1-2.7	0.9-2.9	

DISCUSSION

The initiation of cardiopulmonary bypass with a priming volume of precooled blood (5° to 10° C.) accomplishes two major objectives: first, the rate of total body cooling is greatly accelerated; and, second, rapid cardiac arrest occurs facilitating immediate cardiotomy. A by-product of this technique is the creation of wide temperature gradients (10° to 15° C.) between the slow-cooling lean tissue mass (predominantly skeletal muscle) and the highly vascularized parenchymatous organs. The lag in muscle cooling, combined with cold induced reductions in extracorporeal blood flow (30 to 60 per cent) result in a deficient oxygen supply for the muscle cells. A paradox is thus created, with lean tissue hypoxia occurring in the presence of a high venous oxygen saturation, and a concomitant reduction in the oxygen consumption of all other tissues.

Development of an oxygen debt during perfusion at reduced temperatures and blood flows is greatly accentuated by interruption of the circulation (even at temperatures of 10° C.). The accompanying tissue hypoxia provides the stimulus for anaerobic glycolysis, with the production of lactate and other acid

metabolites. However, the increased hydrogen ion concentration remains sequestered until the onset of rewarming, when a lowered blood viscosity and decreased peripheral resistance permit a resumption of normal flow rates. A rapid wash-out of anaerobic metabolites now takes place, resulting in a metabolic acidosis characterized by an elevated plasma lactate concentration and a fall in arterial pH and plasma bicarbonate.

Under normothermic conditions, there is a maximal rate at which the liver can remove these acid metabolites from the circulation.[10] This rate can be exceeded either by an increase in lactate formation or a diminution in hepatocellular activity. The latter occurs as a physiologic response to hypothermia at liver temperatures below 30° C. and is reversible following rewarming to 37° C. The existence of an inhibition of hepatic metabolism at temperatures of 25° to 30° C. is substantiated by previous investigations.[1] These disclosed the preservation of intracellular glycogen, glucose, and lactate during a 60-minute period of local hepatic hypoxia. This documented alteration in hepatic physiology helps to explain the delay in elimination of accumulated lactate (by oxidation and conversion to glycogen) until the early postoperative period.

In the majority of clinical cases, the metabolic lacticacidosis is well compensated spontaneously. However, in some patients (25 per cent of the series), the occurrence of a reduced cardiac output and arterial hypotension in the immediate postoperative period makes treatment of the acidosis mandatory. Specific therapy consists of the intravenous administration of sodium bicarbonate or of an organic hydrogen ion acceptor, T.H.A.M.* The latter agent is 30 per cent (non-ionized) at a pH of 7.40, and may prove to be an ideal buffer for the increased intracellular lactate accumulation. Continuation of specific antiacidosis therapy is guided by repeated determinations of arterial pH and CO_2 content. Although treatment of the post-hypothermic acidosis is not always successful, this condition was not considered to be the primary cause of death in any patients in this series.

In animals and patients, an elevation in plasma lactate is evident in blood samples obtained after 2 to 5 minutes of cold perfusion. The degree of lacticacidemia present at this stage reflects a period of overbreathing (respiratory alkalosis) which accompanies the thoracotomy. A plausible explanation for the increased intracellular lactate production (in the presence of an extracellular alkalosis) is predicated upon a shift of the oxygen dissociation curve to the left. When this occurs the tissue oxygen supply is diminished, encouraging anaerobic metabolism.[8]

The presence of a pre-perfusion respiratory alkalosis could complicate the maintenance of subsequent acid-base equilibrium in another fashion. An increased rate of intracellular hydrogen ion formation may accompany the alkalosis, partially depleting the intracellular buffers prior to cooling.[13] The resultant decrease in buffering capacity would assume importance in the rewarming phase by compromising the patient's response to the acidosis which certainly will appear.

*Tris (hydroxymethyl) amino-methane, Abbott Laboratories, North Chicago, Ill.

Of final interest is the disturbance in CO_2 transport noted at the lowest temperature during each perfusion. It consists of a significant decrease in CO_2 and P_{CO_2} which occurs in spite of a constant fractional concentration of CO_2 (2 per cent) passing through the oxygenator. Two possible explanations for this hypocapnia must be considered: (1) an increased loss of CO_2 from the blood could occur during passage through the oxygenator at reduced rates of flow, and (2) the combination of physically dissolved CO_2 with sodium ions to form bicarbonate. The latter process is possible since protein ionization decreases with the fall in blood temperature, thus, liberating cations to combine with the available CO_2.[7]

SUMMARY

1. In experimental animals perfused at 10° C. (brain temperature), the total body oxygen utilization is reduced to 16 per cent of the mean control value. During the rewarming phase, the presence of an oxygen debt is confirmed.

2. A lacticacidosis accompanies continuous cold perfusion and is accentuated by intervals of total circulatory arrest.

3. During cooling, the temperature of the skeletal muscle mass lags behind other recorded visceral temperatures (heart, brain, liver, esophagus, and rectum). In the presence of reduced blood flows, this lean tissue serves as a reservoir of accumulated lactate and other anaerobic metabolites.

4. The most severe metabolic acidosis is noted in animals subjected to interruption of the circulation for extended periods of time.

5. A somewhat less marked degree of acidosis is present in the patients cooled to the range of 9° to 14° C.; and a lesser degree of acidosis is evident in other patients perfused at higher temperatures (15° to 23° C.) and at higher blood flows.

6. Lactate metabolism is inhibited during hypothermic perfusion as a result of the marked decrease in hepatocellular activity which occurs below 30° C.

7. Spontaneous compensation for the post-rewarming acidosis occurred in 75 per cent of our patients. In the remainder, postoperative hypotension and reduced cardiac output made specific therapy to control the acidosis mandatory.

We are indebted to Drs. N. Mallick and Mr. J. Carr for their assistance in this study.

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(For Discussion, see page 825)

TREATMENT OF RESPIRATORY INSUFFICIENCY BY PROLONGED EXTRACORPOREAL CIRCULATION

Experimental Observations

Robert Schramel, M.D., William Chapman, M.D. (by invitation), Eugene Weiffenbach, M.D.** (by invitation), and Oscar Creech, Jr., M.D., New Orleans, La.*

IN the course of some diseases of the respiratory system, hypoxia, carbon dioxide retention, and acidosis develop and may not be completely corrected by the usual measures designed to improve gas exchange by the lungs. Although many of these disorders are reversible, death often occurs as a result of pulmonary insufficiency. Among the conditions that may terminate in this way are hyaline membrane disease, status asthmaticus, severe pulmonary contusion and pneumonia, either primary or in association with emphysema or pulmonary resection. The use of a pump-oxygenator for prolonged periods to supplement gas exchange would appear to be a logical form of therapy in these conditions. This report concerns a series of 36 animal experiments in which perfusion by the veno-venous method was carried out for periods of 6 to 24 hours.

PROCEDURE

Mongrel dogs, weighing 10 to 14 kilograms, were anesthetized with intravenous Nembutal, 30 mg. per kilogram of body weight. An 18 Fr. plastic catheter was inserted into the inferior vena cava and this was permitted to drain by gravity into a rotating disc oxygenator. Blood was pumped from the oxygenator into a reservoir suspended 30 cm. above the level of the sternum. The blood then passed through a heat exchanger where it was rewarmed to 99° F. before returning to the animal via another 18 Fr. catheter in an external jugular vein. A cannula was placed in a femoral artery for recording blood pressure, and the electrocardiogram was continuously monitored. In some animals a cardiac catheter was placed in the main pulmonary artery for pressure determinations. An endotracheal tube was inserted through which the animal

From the Department of Surgery, Tulane University School of Medicine, New Orleans, La.

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*U. S. Public Health Service Research Fellow in Cardiovascular Surgery.

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was permitted to breathe room air. In the last 15 experiments the animal was placed on a large Toledo scale in order to aid in maintenance of blood volume (Fig. 1). Samples of arterial blood were drawn preoperatively, 30 minutes after initiation of perfusion, and at hourly intervals thereafter, and oxygen and carbon dioxide content, pH, and pCO_2 were determined. Oxygen and CO_2 content and pH of blood entering and leaving the oxygenator were also determined. Platelet counts and plasma hemoglobin levels were determined in some animals. Urinary output was measured in the last 6 experiments.

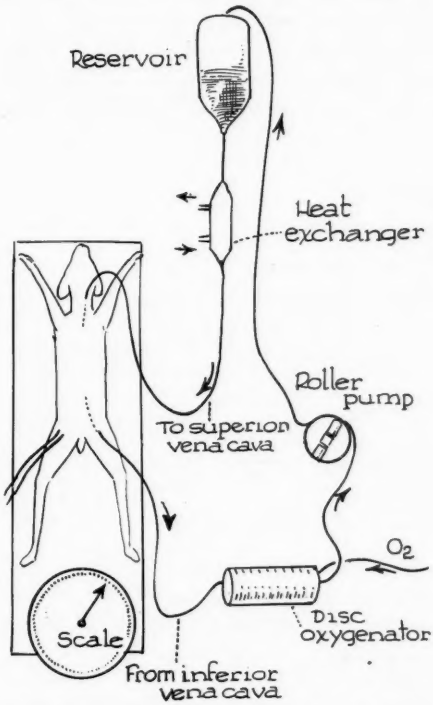

Fig. 1.—Diagram of the procedure employed for veno-venous perfusion.

Blood flow through the extracorporeal circuit was measured by periodically directing flow from the inferior vena cava catheter into a graduated cylinder. Determinations of cardiac output were made prior to perfusion and at hourly intervals by the dye dilution technique. Autopsies were performed on animals failing to survive the experiment and on all surviving animals, 24 hours after termination of the experiment.

RESULTS

The average of eight determinations of oxygen uptake across the oxygenator was 40 c.c. per minute at an average blood flow of 385 ml. per minute (Table I).

Arterial oxygen saturation was not appreciably affected by the procedure, however, since alterations in the rate and volume of respiration were more important in regulation of arterial oxygen saturation. The value of 40 c.c. per minute for oxygen supplied represents about 40 per cent of the oxygen consumption of anesthetized dogs of similar size. The average of fifteen determinations of the change in carbon dioxide content of whole blood across the oxygenator was 50.5 c.c. per minute at an average blood flow of 350 ml. per minute. Examination of the arterial blood at 1 and 2 hour intervals in 24 dogs perfused for 6 hours and in one dog perfused for 24 hours revealed a progressive decline in CO_2 content, ranging from 45.3 vol. per cent preoperatively to 26.89 vol. per cent at the end of perfusion (Fig. 2). Similarly the pCO_2 declined from 47.3 mm. Hg to 28.5 mm. Hg. Despite the marked reduction of CO_2 content there was little change in pH of the arterial blood. The

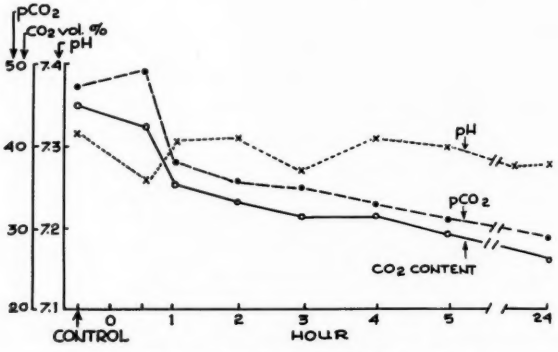

Fig. 2.—Changes in pH, pCO_2, and CO_2 content.

average value for twenty-five preoperative determinations of pH was 7.31. After 6 hours' perfusion the average value was 7.30. In the one animal perfused for 24 hours, pH had declined to 7.28 by the end of the experiment.

TABLE I. GAS EXCHANGE ACROSS OXYGENATOR

	NUMBER OF DETERMINATIONS	AVERAGE CHANGE (C.C./MIN.)	BLOOD FLOW (C.C./MIN.)
Oxygen	8	40.0	385
CO_2	15	50.0	350

Plasma hemoglobin was determined preoperatively and at 2 hour intervals in 15 animals. The maximum plasma hemoglobin in one experiment was 400 mg. per 100 ml. after 4 hours of perfusion, but the average values for the fifteen experiments did not exceed 250 mg. per 100 ml. (Fig. 3).

Platelet counts declined progressively from an average preoperative value of 219,000 per cubic millimeter to 58,000 per cubic millimeter after 6 hours of perfusion. In one animal there were only 10,000 platelets per cubic millimeter after 24 hours of perfusion (Fig. 4).

In some of the early experiments, precipitous decline in blood pressure occurred soon after initiation of perfusion. This effect was most pronounced in experiments utilizing a dispensable bubble oxygenator. It was believed that in most instances this was due to the development of a blood volume deficit despite efforts to maintain pre-perfusion levels in the reservoir and in the oxygenator. In the last fifteen experiments the dog was placed on a scale and its weight controlled within 100 grams of the preoperative weight. In addition,

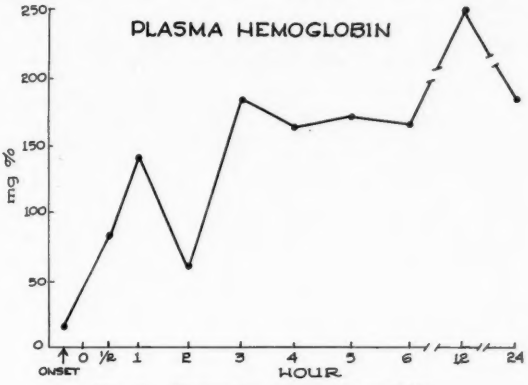

Fig. 3.—Change in plasma hemoglobin.

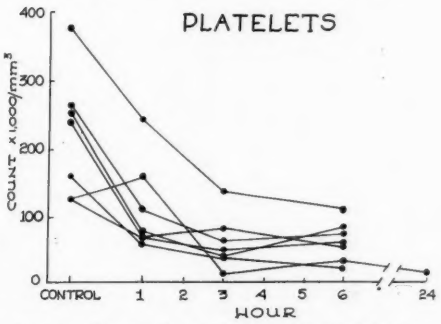

Fig. 4.—Change in circulating blood platelets.

a rotating disc oxygenator was employed. It was possible thereby to achieve stability of both blood pressure and cardiac output throughout the experiment.

Pulmonary artery pressure remained constant unless systemic hypotension developed, in which case a decline of pulmonary artery pressure was also noted.

Eleven dogs failed to survive the experiment. Two of the deaths were believed to be due to blood incompatibility. One dog had fever of 102° F. at the onset of the experiment. The other eight deaths were due to technical difficulties or to gross abnormalities of blood volume. Of the 25 animals surviving, 7 were sacrificed at 24 hours. In all that died spontaneously there were abnormalities in the lungs. The lower lobes were airless and their cut surfaces were fleshy and hemorrhagic. Microscopically there was severe congestion of

all vascular structures and intra-alveolar extravasation of blood (Figs. 5 and 6). In addition there were increased numbers of leukocytes within the pulmonary vessels and focal areas of atelectasis with dilatation of terminal bronchioles were present. Seven dogs were sacrificed at the conclusion of the experiment and the pronounced congestion and hemorrhagic infiltration were not present. The lungs appeared normal grossly with the exception of a few small areas of subpleural hemorrhage (Fig. 7).

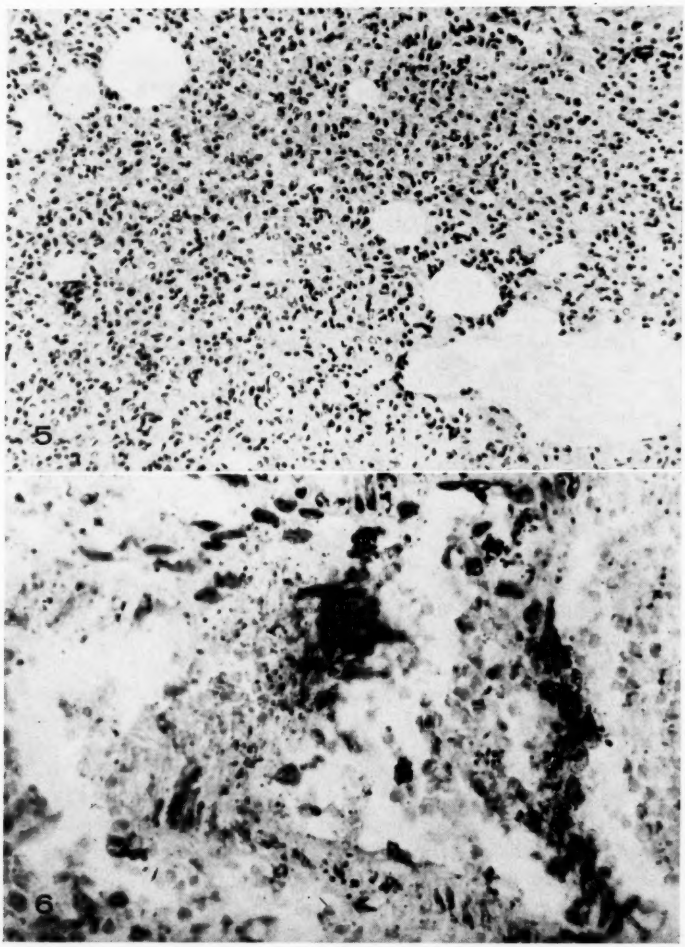

Fig. 5.—Photomicrograph of a section of lung from an animal sacrificed 24 hours after perfusion. There is atelectasis, dilatation of respiratory bronchioles, and congestion of pulmonary vessels (×100; reduced ⅝).

Fig. 6.—Photomicrograph of a section of lung from an animal sacrificed 24 hours after perfusion. Part of the wall of the pulmonary arteriole has been disrupted. This change was infrequent in animals sacrificed at the end of perfusion (×450; reduced ⅝).

When it became evident that abnormalities of acid-base regulation were produced by veno-venous perfusion, measurement of urinary output was begun. An indwelling catheter was placed in the bladder of each of the last 6 animals perfused and there was no urine produced after initiation of perfusion. In one experiment in which perfusion was continued for 24 hours there was no urine formation, although arterial blood pressure and cardiac output were maintained near preoperative levels throughout. The kidneys of this animal showed acute tubular necrosis and extensive plugging of renal tubules with casts (Fig. 8).

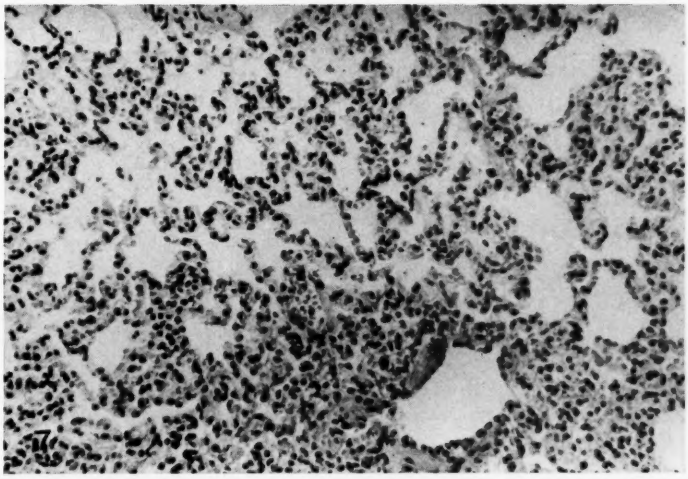

Fig. 7.—Photomicrograph of a section of lung from an animal sacrificed at the end of perfusion. Lung structure is normal. There is no vascular congestion. (×100; reduced ⅜.)

COMMENT

Introduction of oxygen directly into the vascular system in the treatment of respiratory insufficiency has been investigated intermittently since the nineteenth century.[1] The recent development of extracorporeal oxygenators which prevent bubble formation and provide for removal of carbon dioxide makes assisted respiration practical. In 1953, Melrose[2] reported two animal experiments with utilization of veno-venous perfusion for one hour. He recognized that this method should produce no interference with cardiac output. Recently, Krasna[3] described a series of experimental perfusions utilizing a veno-venous technique in which there was elevation of arterial oxygen saturation after experimentally induced hypoxia. There is no question that a significant amount of oxygen can be supplied by this technique. The actual amount in any case will depend upon the oxygen content of venous blood entering the oxygenator, on the performance of the oxygenator, and on the blood flow rate. It should be readily possible to supply 40 per cent of basal oxygen consumption. Both the bubble and disc type oxygenators used in these experiments are excessively efficient in

the removal of carbon dioxide. Over a prolonged period this results in changes in the acid-base equilibrium resembling those seen in fully compensated chronic hyperventilation, that is, reduction in both pCO_2 and CO_2 content with little change in pH. It is of interest that these changes, considered to be characteristic of metabolic acidosis secondary to hypoxic perfusion,[4, 5, 6] can occur despite normal cardiac output delivered with a pulsatile flow and adequate saturation of arterial blood with oxygen.

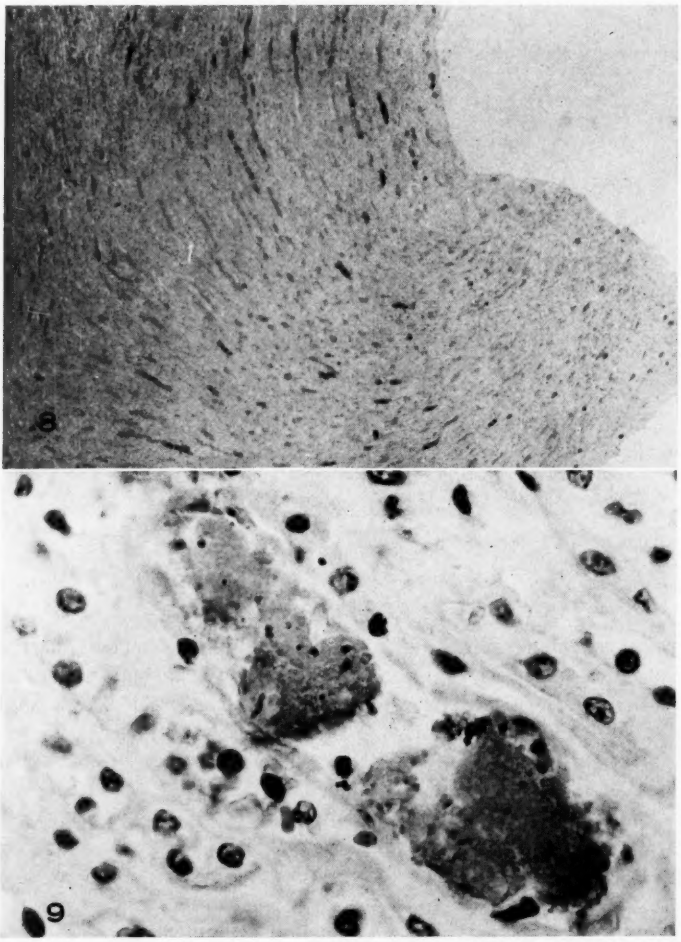

Fig. 8.—Photomicrograph of a section of a renal papilla from an animal which was anuric during a 24-hour perfusion. The renal tubules are filled with granular casts (×50; reduced ⅝).

Fig. 9.—Photomicrograph of a section of kidney from an animal which was anuric during a 24-hour perfusion. A renal tubule contains several casts. Some of the lining epithelial cells are dead and others have separated from the basement membrane (×450; reduced ⅝).

Since several of the animals in this series upon whom pH and CO_2 determinations were performed had developed periods of hypotension or had low values for cardiac output, or had periods of hypoxia (arterial O_2 saturation less than 80 per cent), their data were separately analyzed. It was apparent that there was only slightly greater depression of CO_2 content in these animals than in those undergoing ideal perfusion.

These experiments do not indicate the cause of the depression in CO_2 content. It is of the same magnitude as that observed after short, low flow perfusions using total cardiopulmonary bypass. It occurs despite adequate oxygenation and is greater than the depression observed from anesthesia alone. Further, it is associated with reduction in pCO_2 which may not be wholly compensatory but is due to excessive CO_2 loss from the oxygenator.

The rise in plasma hemoglobin is to be expected in any perfusion of this duration. It is felt that the use of one pump which moves blood from one chamber to another through a single piece of large bore plastic tubing is less traumatic to red blood cells than a system in which blood is pumped through small caliber tubing against arterial pressure, as is done in veno-arterial perfusion. It would have been a more accurate measure of the hemolyzing tendency of the system had plasma hemoglobin levels been determined in the outflow from the oxygenator instead of in arterial blood since the reticuloendothelial system is capable of removing large amounts of free hemoglobin. The blood levels observed (even after perfusion of 24 hours), however, are well within tolerable limits.

Reduction in number of circulating platelets has been described following total cardiopulmonary bypass. Platelet depression continues rapidly for the first hour then levels off at about 50,000 platelets per cubic millimeter. The average value of eight determinations after 6 hours of partial perfusion was 58,000 per cubic millimeter. After 24 hours there were only 10,000 platelets per cubic millimeter. This animal died of massive gastrointestinal hemorrhage—the only significant bleeding episode observed in this series of experiments. A few animals had scattered petechiae in the lungs and in the intestinal tract. With only one major bleeding episode occurring in 36 experiments it would appear that the danger of hemorrhage is not great in veno-venous perfusion of 6 to 8 hours.

Histologic changes occurring in the lungs are disturbing and at present are unexplained. There is a characteristic appearance to the lungs of animals expiring overnight or sacrificed at 24 hours. Congestion and airlessness are present in the lower lobes and are more pronounced in the dependent lung. In addition, small discrete hemorrhagic areas are scattered throughout the aerated portions of the lungs. In animals sacrificed at the conclusion of the perfusion only scattered focal lesions are present. Microscopically there is one consistent pulmonary abnormality consisting of rupture of pulmonary arterioles with intra-alveolar extravasation of blood. Since these findings suggest embolic phenomena, a search was made for embolic material and none was found. Lung

lesions consisting of peribronchial or intra-alveolar hemorrhage have been described in association with total cardiopulmonary bypass.[7, 8] In many instances this has been ascribed to trauma of operation, acute changes in pulmonary blood volume on initiating or stopping bypass, bronchial artery collateral flow, desiccation of lungs from inflation with oxygen during bypass, oxygen toxicity, etc. In this preparation many of these factors are not present, i.e., the subject is breathing room air, lesions have appeared when there is no oxygen supplied to the oxygenator, the thorax is not opened. It has been difficult in these experiments to ensure against acute changes in pulmonary blood volume, particularly when perfusion is initiated. Nonetheless, in several of these experiments, systemic blood pressure has been controlled within narrow limits, cardiac output has remained at or above preoperative levels, and total body weight has been maintained within 100 grams. Despite this, pulmonary hemorrhage of some degree has consistently occurred. It is unlikely that either forward or backward overload of the pulmonary circulation occurred.

The pulmonary changes observed in these experiments are not necessarily a result of extracorporeal oxygenation or even casually related to it. The more extensive lesions seen at 24 hours are probably changes occurring in a dying animal. Similar changes are seen in patients who die after prolonged hospital illnesses. The experimental method permitted the development of at least one significant biochemical abnormality and this may have been responsible for the histologic abnormalities observed in the lungs.

Complete failure of urinary output during the period of perfusion was unexpected. Anesthetized dogs given water ad libitum prior to anesthesia excrete relatively small quantities of urine, that is, 6 to 10 ml. per hour. Histologic studies of the kidneys have not been made in sufficient numbers to determine the extent of renal damage occurring during veno-venous perfusion. There is suggestive evidence that renal blood flow is decreased during total cardiopulmonary bypass,[9] but this may be related to a reduction in total blood flow. Anuria, as observed in these experiments, can best be explained by antidiuresis and studies are now in progress to determine this relationship.

SUMMARY

Partial perfusion by a veno-venous technique has been carried out for 6-hour periods in 36 dogs. Control of blood gas concentrations can be achieved by this method. Progressive decrease of carbon dioxide content of arterial blood occurs when pure O_2 is supplied to the oxygenator. This is associated with reduction of pCO_2. Plasma hemoglobin levels remained within the nontoxic range. Platelets were sharply reduced. Urinary output was completely suppressed during the procedure. Survival of animals for the procedure itself was excellent; however, all but 7 animals died in the immediate post-perfusion period. Lesions were consistently found in the lungs of animals perfused by this method.

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(For Discussion, see page 825)

CORRECTION OF COMPLETE HEART BLOCK BY A SELF-CONTAINED AND SUBCUTANEOUSLY IMPLANTED PACEMAKER

Clinical Experience With 15 Patients

William M. Chardack, M.D. (by invitation), Andrew A. Gage, M.D. (by invitation), and Wilson Greatbatch, M.S. (by invitation), Buffalo, N. Y.

An earlier report by the authors[1] dealt with the feasibility of the long-term correction of complete and disabling atrioventricular block by a subcutaneously implantable, transistorized, and battery-powered pacemaker. From April, 1960, through March, 1961, the device was used in 15 patients. This clinical experience and the modifications in design of the pacemaker and electrode to which it has led form the basis for this communication.

The pacemaker and electrode currently in use are pre-assembled and are implantable as a unit in a one-stage procedure. The pacemaker delivers a biphasic 2 msec. pulse at a pre-set rate (50 to 60 per minute for adults). Power is supplied from ten mercury cells and the circuit has been designed to deliver 10 Ma. against an impedance of 1,000 ohms. This current level has been arrived at on the basis of experimental observations and of numerous measurements made on 8 patients in whom the myocardial electrode was inserted at a first stage and whose heartbeats were paced for several weeks by an external device in order to ascertain stabilization of threshold requirements prior to connecting the electrode to an implantable pacemaker. With the bipolar electrode* used in conjunction with the pacemaker in this series, threshold levels have stabilized around 4 Ma. within a few weeks following implantation. Values above 5 Ma. were seen in instances only in which infection along the electrode tract had occurred. In 2 cases, an opportunity arose to measure thresholds at 5 months and at 10 months, respectively, following insertion of the electrode, and values of 3.0 and 3.5 Ma. were found.

The output of the pacemaker exceeds the threshold by a factor of approximately 2 to 3 but is current limited at approximately 18 Ma., regardless

From the Department of Surgery, University of Buffalo School of Medicine, and the Veterans Administration Hospital, Millard Fillmore Hospital, E. J. Meyer Memorial Hospital, and the Children's Hospital, Buffalo, N. Y.

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*Hunter-Roth patch electrode.

of the impedance offered by the myocardial tissue. This maximum output is lower by a factor of approximately 2 to 3 than the currents with which fibrillation could experimentally be produced with this electrode, either freshly implanted or in the myocardium for a number of months (see Fig. 7).

On the basis of the average current drain observed, the batteries of the unit should yield a usable life of approximately 5 years.* Since the timing circuit is being driven from a lower voltage level than the output circuit, the current drain of the former is greater by approximately 10 per cent. Therefore, failure of a cell of the timing circuit can be expected to occur first and to provide a signal indicating that exhaustion of the battery pack is approaching. An increase in rate of approximately 15 per cent will follow failure of the first battery in the timing circuit and a similar step increase will follow exhaustion of the second.

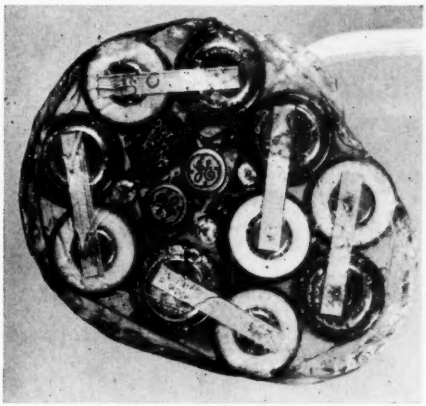

Fig. 1.—Photograph of pacemaker assembly potted in transparent epoxy resin.

The pacemaker is encapsulated in a double shell of silicone rubber† (Fig. 2). The electrode leads connect with the pace maker by two tight-fitting terminal plugs held in place by set screws. These terminals and their receptacles are sterilized prior to assembly of the unit. For replacement of the pacemaker, the device is exteriorized, the seal around the plugs is broken, and, after substitution of a new unit, resealing is done with a room temperature fast-curing silicone compound‡ which can be autoclaved within its container (Fig. 3).

The electrode used in this series of patients was of the bipolar type originally described by Hunter and Roth.[2] In our experience, it has been electrically stable in terms of threshold requirements but, as will be seen below, its mechanical stability is inadequate. It had been our feeling earlier that its electrical

*Estimate based upon ratings of the manufacturer, i.e., 1,000 milliampere hours with a shelf life of 10 years. (P. R. Mallory and Company, Indianapolis, Ind.)

†Dow-Corning Silastic RTV-502.

‡Dow-Corning medical adhesive, Q-3-0149.

stability was related to the bipolar arrangement but subsequent observations have shown us that it is more likely due to the geometry of the high current density obtainable with it. It is possible to use either one of the electrode pins for monopolar driving, the indifferent electrode being a subcutaneous wire, plate, or needle.

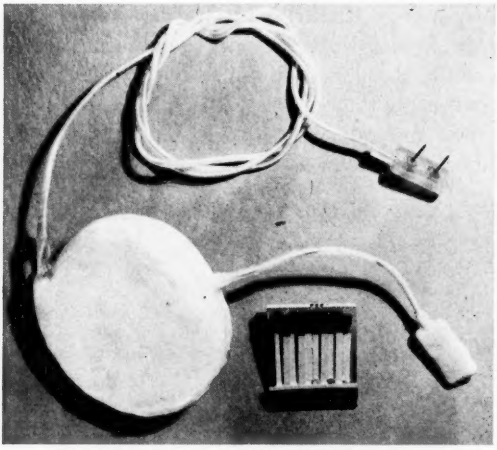

Fig. 2.—Photograph of pacemaker-electrode assembly used in this series—silicone-rubber coated and ready for implantation.

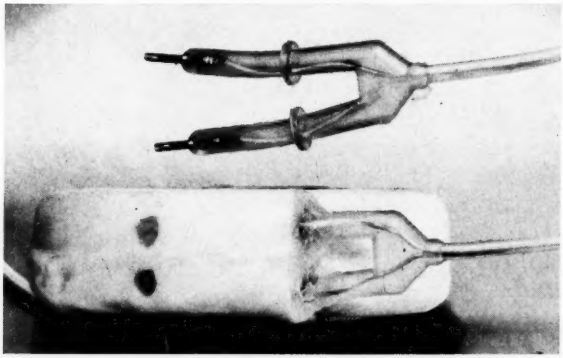

Fig. 3.—Close-up of plug-in terminals connecting electrode lead to pacemaker. Note silicone rubber seal covering junction and set screw sockets.

In view of some of the difficulties we have encountered in actual clinical experience, a safety extension has been added to the unit. It consists of a silicone rubber sleeve containing three wires and a resistor. It terminates in a subcutaneous location at a slight distance from the main pacemaker and electrode wire tracts and, in case of difficulties with pacemaking, it can be exteriorized through a small incision under local anesthesia without undue risk of contamination of the main tracts. From observations obtained by applying an oscilloscope

to the leads depicted in Fig. 4 and the electrocardiographic tracing, one or more of the following may be accomplished: (1) differentiation between pacemaker and electrode failure and, in case of the latter, to ascertain whether it has occurred in both or in only one of the lead wires, (2) to convert to monopolar stimulation if one of the electrode pins is intact, (3) to disconnect the implanted pacemaker and to substitute an external device, if desirable, and (4) to increase current output of the unit from 20 to 40 per cent by removing the resistor, if one is dealing with a rise in the stimulation threshold beyond the capabilities of the unit.

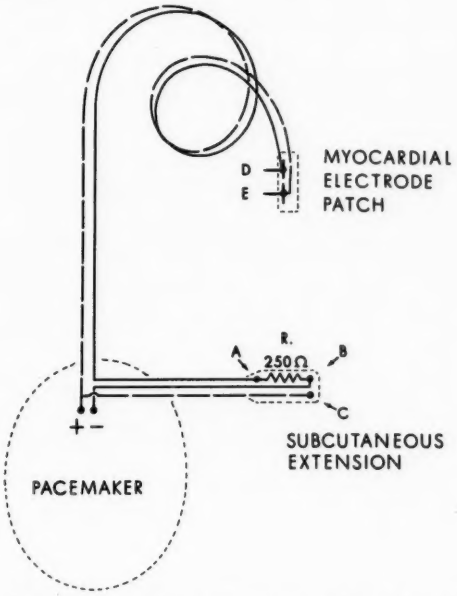

Fig. 4.—Circuit diagram of pacemaker-electrode-safety extension assembly.

The pacemaking rate with this device is obviously fixed and subnormal rates have been used in this series. We believe that rates in excess of 60 (in adults) are contraindicated for the following reasons:

1. Patients with heart block generally do well with a rate of approximately 50, provided the pacemaker remains dependable.
2. A somewhat longer than normal diastolic coronary arterial filling period may be of some advantage to a patient with coronary arterial disease.
3. In this series, moderate physical activity was well tolerated at rates between 50 and 60. In response to exercise, cardiac output can be raised by an increase in stroke volume, a mode of compensation which does not exist at very low rates since, at these, the heart is working at maximum distention when the patient is in the resting state.
4. Finally, experimental and clinical observations by us, as well as others,[3]

TABLE I. FIFTEEN PATIENTS TREATED WITH IMPLANTABLE PACEMAKERS

CASE NO.	PATIENT	AGE	SEX	RECURRENT STOKES-ADAM	SEVERE DISABILITY AND FAILURE	TWO-STAGE OPERATION	ELECTRODE FAILURE	PACEMAKER FAILURE	WOUND INFECTION	CURRENTLY ON PACEMAKER, REHABILITATED	ON PACEMAKER (MO.)
1	FH	77	M	Yes	Yes	Yes				Yes	12
2	ID	58	F	Yes	No	Yes	Yes	Yes		No	–
3	MP	65	F	Yes	Yes	Yes		Yes		Yes	11
4	JP	64	M	Yes	Yes	Yes	Yes			Yes	11
5	AT	37	M	Yes	Yes	Yes			Yes	Yes	9
6	JZ	72	M	Yes	No	Yes			Yes	No	–
7	LK	63	F	Yes	Yes	Yes				Yes	9
8	AW	68	M	Yes	Yes	Yes				Yes	6
9	FJ	68	M	No	Yes					Yes	5
10	RM	62	M	Yes	Yes					Yes	1
11*	BJ	66	M	Yes	No					Yes	1.5
12*	PH	58	M	Yes	Yes					Yes	4
13*	JB	7	F	No	Yes	Yes				Yes	5
14	RS	57	M	Yes	No		Yes			No	–
15	GS	65	M	Yes	Yes					Yes	1.5

*Case 13 was treated in association with Dr. N. Thompson, Children's Hospital, Buffalo, New York. Cases 11 and 12 were part of a VA cooperative study on Coronary Arterial Disease. These patients were operated upon at the VA Hospitals in Coral Gables, Florida, and Albany, New York.

indicate that the duration of asystole which follows the sudden withdrawal of an electrical pacemaking stimulus increases in proportion to the rate at which this artificial electrical pacemaking was carried out. Periods of asystole of the order of 15 to 20 seconds may be encountered following the sudden cessation of electrical pacemaking at approximately normal rates (Fig. 5). While such a period of cardiac arrest can be tolerated by an otherwise healthy experimental animal, there is considerable doubt whether it would be equally innocuous in an elderly patient with generalized arteriosclerosis. The use of subnormal rates certainly favors early resumption of the idioventricular activity should sudden failure of the artificial pacemaker occur.

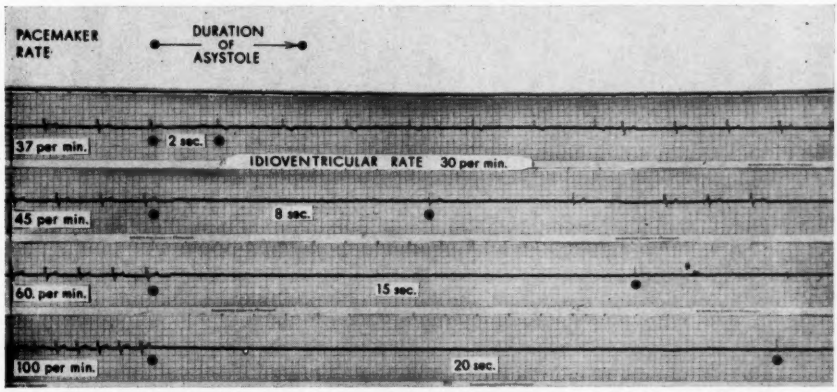

Fig. 5.—Electrocardiographic tracing taken on a dog with surgically induced atrioventricular block. The animal's heartbeat was paced at increasingly higher rates. The dot on the left marks the time at which the artificial stimulus was suddenly withdrawn. The dot on the right marks the time at which the first spontaneous idioventricular beat appears. Duration of asystole following sudden cessation of pacemaking increases in proportion to the rate at which pacing was carried out.

CLINICAL EXPERIENCE

Fifteen patients have been operated upon from April 18, 1960, through March 16, 1961. Pertinent statistical data on this series have been summarized in Table I. In all patients, the atrioventricular block had been complete and had been present for periods varying from several months to several years. In nearly all of the cases, the clinical pattern was one of Stokes-Adams attacks recurring with increasing frequency and uncontrollable by drugs. The gravity of the situation in these patients is illustrated by the fact that, in 7 of 15, periods of complete unconsciousness in excess of 24 hours had occurred. Most had been severely disabled by total loss of exercise tolerance and cardiac failure, the latter being the primary indication for operation in 2 cases (Cases 9 and 13).

OPERATIVE PROCEDURE

It is mandatory that monitoring equipment, as well as facilities for external pacemaking, be in place prior to induction of anesthesia. Earlier in the series,

an anterior thoracotomy through the bed of the fifth rib and cartilage was used; more recently, an anterolateral approach was employed for better exposure of the left ventricular myocardium. The pericardium was incised and an avascular area as high as possible on the left ventricular wall exposed. It is important to have some means available by which pacemaking can be carried out during the interval between entrance into the pleural cavity and the actual insertion of the pacemaker electrode. This can be conveniently accomplished with two sterile clip leads, several feet long, connected to the terminals either of the implantable pacemaker or of a second external device with suitable current output. One lead is fastened to the rib spreader and the other to a hemostat with which the surface of the heart may be touched for stimulation, if required.

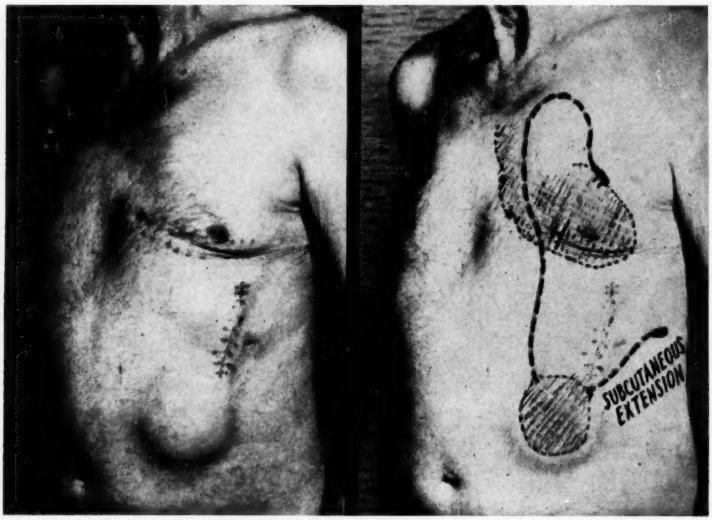

Fig. 6.—Photograph of patient with implantable pacemaker and diagram of the pacemaker-electrode assemply as it resides in the body. (In the more recent cases, a spare electrode was inserted as a precaution against failure.)

After exposure of the myocardium, the thoracic field is then temporarily abandoned and a subcutaneous pocket for the implantable pacemaker is made through a small incision in the left upper quadrant. A small tunnel for the subcutaneous extension is formed by blunt dissection and a second tunnel is made connecting the abdominal and thoracic incisions. The implantable pacemaker is pushed into the subcutaneous pocket and the electrode and leads are then passed into the thoracic cavity and affixed to the left ventricular myocardium. The pleural cavity, as well as the small pocket in which the pacemaker resides, is drained under mild suction for 24 to 48 hours postoperatively.

RESULTS

One patient (Case 2) died 8 months following the initial operation. Six months postoperatively, she experienced a Stokes-Adams attack from which

she recovered and which was traceable to an open circuit in the electrode. A new electrode was placed and connected to the subcutaneously implanted pacemaker. Two months later, she suddenly died. For one week prior to her death, she had complained of episodes of dizziness and she had been seen on several occasions during this period. The pacemaker was functioning well on these occasions and her pulse was found to be at the expected rate. Her complaints were erroneously attributed to a concomitant eye condition. She had been taught to check her own pulse several times during the day but was somewhat reluctant to do so. Her family stated that she had complained of dizzy spells for several hours prior to her death. She appeared to have had a typical Stokes-Adams attack from which she did not recover. An electrocardiographic tracing obtained shortly thereafter failed to reveal the pacemaker signal, although the latter was present when a repeat tracing was obtained at the time of post-mortem examination. The pacemaker appeared to be functioning properly then but continuous observation for a period of several weeks showed an intermittent dysfunction which subsequently was traced to a faulty capacitor. It is likely that the episodes of dizziness preceding her death were caused by intermittent pacemaker malfunction with a fatal Stokes-Adams attack supervening during one of these episodes.

Of the remainder of the patients, 9 have made a completely uneventful recovery and their complete rehabilitation has been most gratifying. In the remaining 5 patients, the following complications and difficulties have occurred.

CASE 5.—Staphylococcus infection occurred in pacemaker pocket 2 months postoperatively. This was corrected by temporary exteriorization of pacemaker and implantation at a different site.

CASE 6.—Staphylococcus infection occurred 2 weeks postoperatively involving pacemaker pocket and electrode tracts. The latter became chronically infected and the electrode had to be removed.

CASE 4.—Electrode failure took place 8 months postoperatively and was corrected by insertion of a new electrode. Subsequent course has been good.

CASE 14.—Electrode failure occurred 2 months postoperatively. Since this occurred quite recently, correction has been deferred pending completion of tests on a new electrode to be described below.

CASE 3.—Pacemaker failure took place 10 months postoperatively manifested by an increase in rate and was corrected by replacement of the pacemaker. Analysis of all the components of this faulty unit has not been completed at this writing; however, preliminary evidence points toward a faulty transistor as the cause of failure.

In summary, then, in 12 of the 15 patients pacemakers are currently in use. In 9, the recovery was uneventful. In 3 difficulties have been encountered but were corrected and, ultimately, a good result was achieved. An analysis of our complications and difficulties shows them to fall into three categories—infection, electrode failure, and pacemaker malfunction.

Both wound infections have occurred in patients in whom a two-stage procedure was employed, with the electrode wire temporarily traversing the skin. We believed that the staged operation was necessary in the beginning in order

to obtain evidence on threshold stabilization. No infection has occurred in the group of patients in whom the pacemaker-electrode assembly, gas sterilized, was implanted in a one-stage procedure, which, we believe, will minimize the risk of this type of complication.

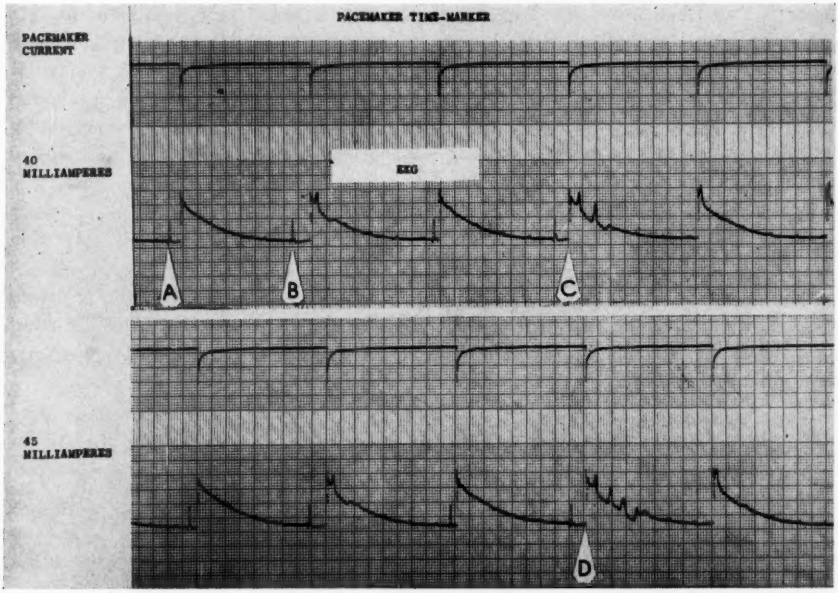

Fig. 7.—Electrocardiographic tracings from an experimental attempt to produce fibrillation with the pacemaker in a dog with surgically induced atrioventricular block. The pacemaker was set at a slightly slower than idioventricular rate, its stimulus falling into various parts of the cardiac cycle following the preceding idioventricular beat. Fibrillation thresholds ranged from 38 to 60 Ma. in six experiments. (When the heart was driven completely by the artificial pacemaker, fibrillation could not be obtained with current of up to 250 Ma.)

A and *B:* Idioventricular complexes.

C and *D:* Aborted runs of ventricular fibrillation induced by pacemaker stimulus falling into vulnerable period following preceding idioventricular event. Marked base-line deflection is caused by high pacemaker current.

Two instances of pacemaker malfunction due to component failure have been encountered in spite of an elaborate environmental and electrical testing program designed to detect flaws which subsequently may lead to failure. At first glance, this appears to be a high rate of failure but it must be considered that this has occurred only twice in well over 100 units built for experimental and clinical purposes during a period of almost 3 years.

The most disturbing problem has been the mechanical failure of the bipolar patch electrode. This is related to the considerable strain and motion of the electrode assembly within the body, resulting in material fatigue and wire disruption. In addition to the above-mentioned instances, this type of failure has also occurred in 2 experimental animals. The discontinuity in the lead wire appeared to be gradual, leading at first to intermittent conduction and, subsequently, to a completely open circuit.

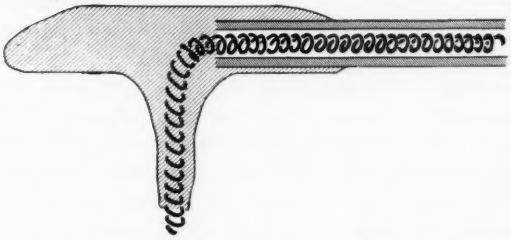

Fig. 8.—Drawing of helical spring electrode. Note that the coil rides free in the insulating sleeve up to the level of the electrode patch. Electrode pin and lead are made of one piece.

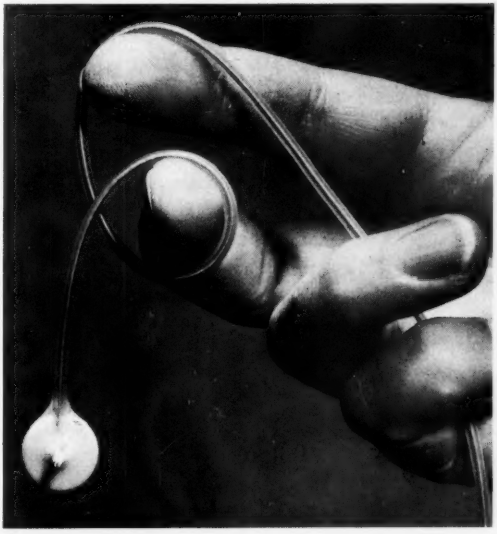

Fig. 9.—Photograph of platinum coil electrode.

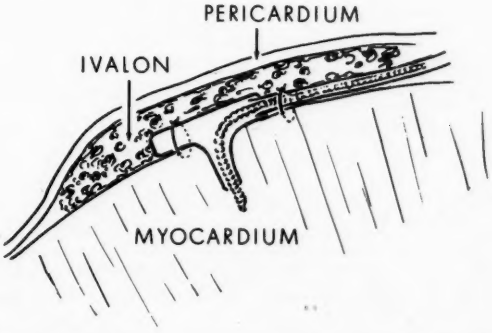

Fig. 10.—Diagram of platinum coil electrode and method of fixation.

Obviously the electrode problem is of paramount importance for successful pacemaking on a long-term basis, whether it be by an implantable or by an external device. In order to gain some information on the precise motion and deformation to which the electrode assembly is subjected within the body, detailed cineradiographic studies were made in 4 patients. These revealed, in addition to some flexing, a rather abrupt type of whiplash motion at the electrode patch itself, which was due to ventricular contraction and resulted in an elongation type of stress. For a conductor to withstand these stresses (at a rate of approximately 30 million cycles per year), not only resistance to flexing but also tolerance to elongation appear to be necessary. To meet these requirements, a different type of electrode was designed. Briefly, the conductor is a helical coil spring made from a 0.01 inch gauge platinum-iridium alloy wire.* The outer diameter of the coil measures 0.040 inch and it rides freely in an insulating sleeve of silicone rubber. The two coils (used for bipolar driving) end in separate silicone rubber patches in which they make a right turn and then terminate as the electrode pins. Thus, the entire assembly is made of one piece and possibilities for error in the manufacture are eliminated (Figs. 8 and 9).

For insertion of the electrode into the myocardium, a small stab wound is made through the epicardium which permits the pin to be pushed in with ease. It is then held in place by a few sutures and both electrode patches are covered with a piece of Ivalon sponge which holds the electrodes in place between the epi- and pericardium (Fig. 10). Electrical thresholds seen with this type of electrode in experimental animals compare favorably with those observed with the old type of bipolar patch and we hope that this design will minimize the problems associated with electrode breakdown.

SUMMARY AND CONCLUSIONS

1. A transistorized and subcutaneously implantable pacemaker has been used for the correction of complete and disabling heart block in 15 patients.

2. Indications for operation were severe disability from loss of exercise tolerance but were chiefly life-threatening recurring Stokes-Adams attacks uncontrollable by drug therapy.

3. Uneventful recovery and complete rehabilitation was achieved in 9 patients. In 6 patients, complications and difficulties were encountered but correction of these was possible in 3 of the 6. One patient died 9 months following operation. Twelve patients are currently having their heartbeats paced. Follow-up studies range from one to 12 months.

4. Modifications in the design of the pacemaker and the electrode based

*Platinum-gold, platinum-iridium, and stainless steel wires have been used in the manufacture of this coil. There does not appear to be much difference in the mechanical characteristics of coils made of these alloys. Their respective properties in regard to corrosion are currently under long-term experimental study. Accelerated fatigue tests have been done on a 0.018 and 0.01 inch platinum-gold alloy wire by applying a severe flexing strain to a ¼ inch long coil at 282 and 360 cycles per second. Under the conditions of this test, the heavier coil was exposed to 7.5 million cycles and found to be intact at that time. The finer gauge coil broke after 30 million cycles. Further fatigue testing at more realistic stresses and cycling rates is now in progress.

We are indebted to Dr. Robert Ketter, Professor and Chairman of the Department of Civil Engineering at the University of Buffalo, for his assistance with these tests.

upon this initial clinical experience have been described. An electrode designed to withstand the precise stresses it is subjected to within the body has been described.

5. Rehabilitation in the 12 patients successfully treated was gratifying and impressive since these patients lead an entirely normal life without the restrictions and inconvenience imposed by an external appliance. Further evaluation of this form of therapy appears warranted in selected and disabled patients.

ADDENDUM

OCTOBER 18, 1961.—Since completion of this report, 17 patients have been operated upon, bringing our total experience to 32 cases. The pacemaker failure in Case 3 was caused by a premature battery exhaustion rather than a faulty transistor as indicated in the text. In addition to Case 2 listed above, 3 patients have died from coronary occlusion (1, 3, and 20 days postoperatively).

In the first 16 patients, the Hunter-Roth electrode had been used and our above-stated misgivings about its mechanical stability have been borne out as time went on. Wire disruption and/or corrosion have led to ten failures, easily corrected in most instances because we usually had left a spare electrode. In the last 16 cases, we have exclusively used the platinum-iridium coil electrode, and, in 3 earlier cases, it was used as a replacement for a defective Hunter-Roth electrode. In these 19 instances, we have not had any electrode failures, with a follow-up range from 1 to 7 months and a mean of 4 months.

Over-all results in this series were gratifying, with 27 of the 28 survivors currently "pacemade" and rehabilitated. Correction of one electrode failure was deferred because of a considerable improvement in the patient's idioventricular rate after several months of pacemaking. The follow-up in the series ranges from 1 to 18 months with a mean of 8 months.

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DISCUSSION

(PAPERS BY YEH [PAGE 782], BERNHARD [PAGE 793], SCHRAMEL [PAGE 804], AND CHARDACK [PAGE 814] AND THEIR ASSOCIATES)

DR. WATTS R. WEBB, Jackson, Miss.—I want to comment on the papers by Dr. Yeh and Dr. Bernhard on the metabolic changes in profound hypothermia. The clinical use of profound hypothermia has outrun physiologic experimentation and we are only now beginning to catch up to a small degree, although certainly not as much as we need to.

We have done similar experiments on profound hypothermia and circulatory arrest. In general, our changes in pH and lactic acid changes have been very comparable to those reported by Dr. Gross' group.

[Slide] We have also evaluated the electrolyte changes that occur in the serum and in serial biopsies taken from the liver, from the heart, and from the abdominal wall muscle.

The method has been to cool dogs to 5° C., allow one hour of complete circulatory arrest, and then rewarm. During the one hour of arrest, the temperature drifts up to 10 or 12 degrees. You will notice that the electrolyte changes in the serum sodium are rather minimal.

The chloride shows fairly marked changes during the period of circulatory arrest, returning toward normal with rewarming. Notice that the calcium and potassium show reciprocal changes during this period.

[Slide] This slide shows the changes in the sodium. You will notice in the liver a great rise, from about 45 to nearly 90 mEq. per kilogram of tissue during cooling, but a fall toward normal during rewarming.

In the heart muscle, there is a continuous rise in sodium; in the skeletal muscle less profound changes occur.

[Slide] The changes in the potassium are reciprocal to the sodium so far as the liver is concerned, with a drop which never returns to normal. There is an early increase both in the heart and in the skeletal muscle with a return toward normal on rewarming.

[Slide] This shows the changes in chloride which, again, are reciprocal to the others, with a marked fall in most of the tissues but a return toward normal at the end.

We were impressed with the great degree of alterations that occurred in all these modalities, emphasizing to us the many factors that still need further evaluation. At this time, from our clinical and experimental experience, it seems to us that a moderate degree of hypothermia, with continuing low flow rates, is far preferable to hypothermia arrest as studied here.

DR. W. F. BALLINGER, II, Philadelphia, Pa.—Our studies have paralleled those of Dr. Bernhard in the investigation of hypothermia, with one exception. We have utilized the concept of excess lactate, as originally described by Huckabee, which allows us to determine that lactate which is produced only by anaerobic metabolism and to ignore that lactate which is produced by other causes, such as, hyperventilation, infusion of glucose, and so forth.

We found a consistent rise in excess lactate during cooling both in humans and in dogs. This was accompanied by a fall in pH, with little, if any, change in arterial pCO_2. During the period of stable hypothermia, the temperatures of the cooler viscera and the warmer muscle mass became the same and excess lactate was removed.

We had evidence to indicate that this may occur in the liver, since previous investigations showed the liver cleared excess lactate during hemorrhagic shock. [Slide] We then prepared animals so that all venous blood from the hind extremities was diverted into the portal vein. All tributaries to the portal vein were ligated so that only venous blood from the hind extremities passed to the liver. All hepatic venous blood was then diverted to a pump oxygenator and back to the hind extremities. Heat exchangers were incorporated into the system so that blood entering the liver or legs could be cooled separately.

If the temperature of the liver and the legs were approximately equal, the production of excess lactate in the periphery was equal to its removal by the liver. On the other hand, when the legs were warmed and the liver cooled, you can see that the production of excess lactate exceeded its removal by the liver and the reverse was true when the liver was warmed and the leg cooled. Thus, a metabolic acidosis develops during cooling.

During warming, a second type of acidosis developed, characterized by an elevation of pCO_2 and a fall of pH. Excess lactates continued to decrease. The rise in pCO_2 was due to the increased metabolism occurring in the periphery, combined with the decreased solubility of CO_2 during warming.

DR. WILLIAM E. NEVILLE, Cleveland, Ohio.—George Clowes and I have been intensely interested in profound hypothermia with complete circulatory arrest and employed it clinically on occasion with benefits. However, due to the deleterious effects which can occur when it is not used judiciously, we have not employed it routinely (A. M. A. Arch. Surg. 89: 108-119, 1961).

In the laboratory and in patients we have investigated the metabolic aspects of profound hypothermia and arrest and can only concur with the results presented by Drs.

Bernhard, Schwarz, and Gross. There is no question that at 10° C. hypoxic acidosis can occur; although the mean oxygen uptake at this low temperature is less than 1 c.c. per kilogram per minute, the tissues can incur an oxygen debt if they are not adequately perfused or if the circulation is interrupted for long periods of time. The acidosis is not manifest until the rewarming periods and can be more severe when temperature gradients exist between the esophagus and the rectum.

[Slide] On this slide the mixed venous oxygen content is plotted against the duration of circulatory arrest in two groups of dogs. In Group A, the temperature of the esophagus and rectum was equilibrated at 10° C. and in Group B a temperature gradient of from 7° to 10° C. existed between the upper and lower parts of the body. As you can see, at the end of 40 minutes of complete circulatory arrest in the dogs of Group A with the temperature equilibrated at 10° C., the mixed venous oxygen content, the A-V difference, had fallen only 3 volumes per cent, whereas, when temperature gradients exist, at the end of 38 minutes of complete cessation of the circulation, almost 8 volumes per cent of oxygen have been extracted by the tissues.

[Slide] This depicts the pH values in four groups of dogs which were cooled to 10° C. by extracorporeal perfusion with a pump oxygenator and rewarmed to 37° C. In the first group the circulation was not arrested at low temperatures. The pH values which were corrected for temperature remain essentially unchanged, indicating that acidosis did not occur during the rewarming phase. The same is true in Group 2 in which there was circulatory arrest for only 15 to 30 minutes. In sharp contrast are the pH values in Groups 3 and 4 in which the circulation was arrested for long periods of time or the animals were perfused at a very low flow rate of 10° C. for an hour before being rewarmed. These dogs all became markedly acidotic during rewarming and, despite vigorous treatment with sodium bicarbonate, etc., they died as the result of a severe uncompensated metabolic acidosis.

[Slide] This last slide is on a phase of profound hypothermia with arrest which has not been entirely elucidated; that is the decrease or decay in oxygen tension in the brain during complete circulatory cessation. Due to the inaccuracies in measuring the pO_2 of the brain tissue per se, we have taken the pO_2 of the cerebrospinal fluid as an index of what is occurring in the brain substance. Together with our neurosurgeon, Dr. Bloor, we have measured the pO_2 of the cerebrospinal fluid during perfusion and arrest by means of an oxygen electrode needle inserted into the great cistern of the brain. On this slide is shown the decay in the pO_2 of the cerebrospinal fluid observed during total arrest of the circulation at 37° C., 20° C. and 10° C. As would be expected as the temperature is lowered, there is a progressive increase in the time necessary for oxygen tension in this fluid to fall to values near zero. At 37° C. the oxygen tension was near zero within 2 minutes. At 10° C., in 11 animals the average period required to produce a comparable fall was 18.5 minutes; however, it was 41 minutes before there was no measurable oxygen in the fluid.

Thus, if one is going to use this modality, he must be aware of the fact that metabolic acidosis or irreparable brain damage can result when the circulation is totally interrupted for periods beyond 30 to 40 minutes.

DR. NAZIH ZUHDI, Oklahoma City, Okla.—We have been using at Mercy Hospital, Oklahoma City, a perfusion system which uses the principle of true hemodilution. In other words, our heart-lung machine is definitely primed with 5 per cent dextrose in water and this priming volume is pumped into the patient while the patient's own blood is filling the heart-lung machine. In this manner, true hemodilution occurs. *Neither machine nor patient is primed with blood.* Routine banked citrated blood is used to replace the usual loss from the surgical field.

[Slide] The basic features of our perfusion system include: (1) internal hypothermia, moderate (25° to 30° C.), (2) low flow rates of 20 c.c. per kilogram of body weight per minute; these flow rates are adequate for our system as determined with physiologic studies and survival of dogs and humans, and (3) hemodilution—the priming volume of the machine with 5 per cent dextrose in water is accomplished using the formula *kg weight* × *2* × *24*,

and corresponds to one third of the 24 hour fluid requirement. The priming volume varies with the weight of the patient.

[Slide] The system is mainly a modified DeWall bubble oxygenator with a double helical reservoir. The inner stainless steel helix acts as a heat exchanger by circulating water through it at different temperatures. This heat exchanger is volume decreasing as opposed to the usual volume increasing heat exchangers. Venous drainage and cardiotomy suction blood are returned by gravity. In this manner, only one pump head is used on the arterial side.

[Slide] What happens to this 5 per cent dextrose in water which is pumped into the patient? It does remain in circulation and this was shown by recording radioactivity through a side limb on the venous return tube, the side limb passing through a scintillation well.

[Slide] The plasma hemoglobin rise in 43 consecutive patients was of 18.9 mg. per cent, the range being 8.3 to 47.6 mg. per cent.

The double helical reservoir heart-lung machine in all its modifications has been used on 133 patients and on 86 patients exactly as herein described. Dogs do well and patients do well.

DR. JOSEPH M. FORD, New York, N. Y.—I should like to congratulate Dr. Chardack on the use and development of a subcutaneous transistorized pacemaker. This will probably obviate the danger of prolonged and chronic infection reaching the pericardium. We have had experience with 10 patients on whom myocardial electrodes and the extracutaneous metronic transistorized pacemaker has been used. This experience extends over a period of 23 months.

One of these patients had undergone operation by Dr. Cartwright in Albuquerque before he joined us. Each of these patients had a complete A-V distortion with a resultant bradycardia and consequent Stokes-Adams seizure. None of these patients would respond to excellent medical management.

Of these 10 patients, 3 died. One patient 76 years of age, died when a progressive autogenic process caused a pericardial abscess and complete extrusion of the electrodes. He died 5 months after operation.

The second patient, 63 years of age, died in a seizure 3 months after operation at a time when the conduction system was interrupted. We believe that one of the wires was broken.

The third patient was an 81-year-old man who died 5 days after operation in complete renal failure.

So we have 7 remaining patients. They are all doing well. One of these patients, 73 years of age, has reverted to a sinus mechanism with a rate of 76. His pacemaker is turned off but he refuses to allow us to detach it. Perhaps he is right.

DR. HOWARD A. FRANK, Boston, Mass.—Our team had been working for some 4 or 5 years in the laboratory on the problem of the threshold for direct myocardial stimulation when we were encouraged by the clinical success of Dr. Hunter in St. Paul and Dr. Chardack with the Hunter electrode. Both Dr. Hunter and Dr. Chardack were kind enough to exchange ideas with us and tell us of their experience, and we were thus encouraged to apply our own electrodes and pacemaker clinically. We implant the electrodes in the wall of the left ventricle and the pacemaker subcutaneously, in one stage or two, and now have 14 patients of our own and some 8 others done by colleagues.

Based on our laboratory experiments and also on our feeling that the Hunter electrode base is too rigid (I am interested to hear that Dr. Chardack now thinks so, too), and perhaps that there is rather more foreign material than we like to put in the pericardial sac, we use two separate segments of purified platinum wire embedded in the wall of the ventricle. [Slide] This is our electrode system. In laboratory experiments purified platinum worked best, and these electrodes have held up well clinically.

[Slide] The pacemaker box is smoothly contoured, and covered with a nonirritating expoxy resin. It is just over 2 inches square and is 5/8 inch thick. Everyone would like to make these things smaller and, in these days of minute electronic equipment, one wonders why one can't. The size depends mainly upon the battery space required to provide the amount of electrochemical energy you wish the unit to have, and this in turn depends on the rate and duration of stimulation you would like the unit to provide, the current strength and duration for each individual stimulus, and the safety factor that you would like to build in.

Our experience extends over 10 months. All of our patients are doing well. We have not had to interrupt pacing because of rise in stimulus threshold. We have had electrode wire or pacemaker unit difficulties in several patients, remedied by appropriate adjustments of the electrical units. Our experience in full and our views on the various techniques available for electrical pacing of the heart are given in the Annals of Surgery (in press). Although a number of technical difficulties remain to be overcome, we are convinced that this is a highly satisfactory method for protecting patients with this distressing and dangerous disease.

DR. ADRIAN KANTROWITZ, Brooklyn, N. Y.—[Slide] For the past 2½ years we have been working with the Advanced Circuits Division of the General Electric Company on various bioelectronic devices. This is a pacemaker developed by the General Electric Company and consists of only four batteries in this model. Some have five battery models. It is approximately an inch and a half in diameter and one-half inch thick. I am told by the engineers that this should last about 5 years.

We are using the American Cyanamid wires which consist of 49 strands of stainless steel encapsulated in a Teflon cover.

[Slide] We have implanted this pacemaker in a 46-year-old woman who had total heart block, and it has paced her heartbeat now for 8½ months.

In addition to an intrinsic rhythm of its own, it is possible to alter the rhythm by a radio link from the outside. If I plug this pacemaker into this flashing circuit, the intrinsic rhythm of the pacemaker itself will be demonstrated [Demonstrating]. This is set at 64 beats per minute. In addition, we have the external circuit with which we can control the rate, anything up to 220 beats per minute; this has to be brought within 2 or 3 inches of the pacemaker. When it is removed, the pacemaker again will revert to its own intrinsic rhythm.

DR. PARRY B. LARSEN (for DR. WILLIAM W. L. GLENN), New Haven, Conn.—We would like to inform the Association of the present status of remote stimulation of the heart by radiowave transmission to a simple receiver buried beneath the integument. [Slide] This receiver is buried beneath the skin over the lower part of the mid-sternum. Electrode wires lead from the receiver to the ventricle. [Slide] The radiowave transmitter has recently been transistorized so that it may be carried in the patient's breast pocket.

[Slide] The antenna leads from the wave generator to the skin overlying the buried receiver.

The advantages of this method of remote stimulation of the heart are twofold: (1) a simple design by Dr. Alex Mauro may hopefully remain trouble-free for long periods, and (2) the rate and intensity of the stimulus are under direct external control.

Our clinical experience with radio frequency stimulation of the heart is limited to 4 patients with Stokes-Adams syndrome. The results have been encouraging but there still may be the problem of fracture of the electrode wire. We use 47 strands of 40 stainless steel for each electrode, but we are by no means certain that this will hold up for the many years that may be required.

The new spring electrode described by Dr. Chardack and his associates may well prove to be marked improvement over the previous methods, but we would feel happier if the spring were not a monofilament.

DR. I. KREEL, New York, N. Y.—I should like to report a similar study which was carried on at Mt. Sinai Hospital over the past year and a half and of which there was a preliminary report made several months ago.

[Slide] The type of setup we have used is demonstrated here. There is a veno-venous perfusion with drainage from the inferior vena cava and a pumping back into the superior vena cava. These animals are first rendered hypoxic by forced ventilation through an intratrachial tube, using a 12 per cent oxygen mixture. After hypoxia is induced, it is measured by arterial oxygen saturation, the perfusion is turned on, and the ability of the perfusion to reverse the hypoxia is measured.

[Slide] You see here a chart of the arterial oxygen saturation before and after the perfusion, the cross marks being the anoxic level, and you will note that these dogs may be rendered quite hypoxic, and that, in virtually all cases except this one, over a 20-hour period of perfusion the oxygen saturation was maintained at normal or near normal levels throughout; you will note also that this was true virtually, regardless of the level of hypoxia which was induced.

[Slide] This represents a study of the pH changes, particularly this lower half. During the period of anoxia you will note the pH fell considerably. You will note also that, as the animal was kept on the perfusion and the oxygen saturation corrected as demonstrated above, the pH change was also corrected and levels near normal were maintained for long periods of time.

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